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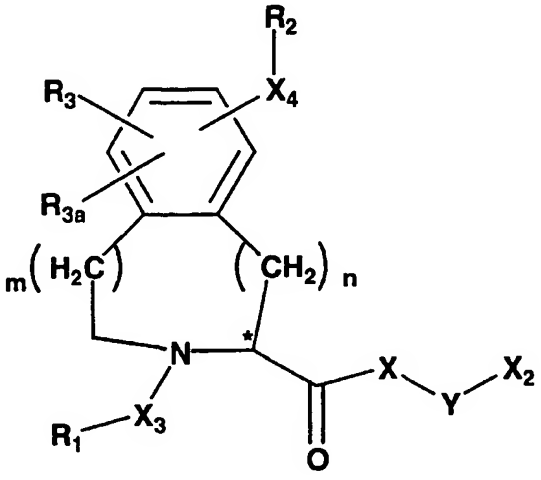
(54) Title: TETRAHYDROISOQUINOLINE ANALOGS USEFUL AS GROWTH HORMONE SECRETAGOGUES



(I)

(57) Abstract: Tetrahydroisoquinoline analogs are provided which are useful in stimulating endogenous production or release of growth hormone and in treating obesity, osteoporosis (improving bone density) and in improving muscle mass and muscle strength. The tetrahydroisoquinoline analogs thereof have the structure (I) wherein R_1, R_2, R_3, R_{3a}, X_1, X_2, X_3, X_4, m and n are as described herein.

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TETRAHYDROISOQUINOLINE ANALOGS USEFUL AS GROWTH HORMONE SECRETAGOGUES

Field of the Invention

The present invention relates to novel tetrahydroisoquinoline analogs which are growth hormone secretagogues, that is they stimulate endogenous production and/or release of growth hormone, and to methods for treating obesity and diabetes, improving bone density (to treat osteoporosis) and stimulating increase in muscle mass and muscle strength employing such compounds.

Background of the Invention

The pituitary gland secretes growth hormone which stimulates growth in body tissue capable of growing and affects metabolic processes by increasing rate of protein synthesis and decreasing rate of carbohydrate synthesis in cells. Growth hormone also increases mobilization of free fatty acids and use of free fatty acids for energy.

The prior art is replete with patents/applications which disclose compounds which are useful as growth hormone secretagogues.

The following patents/applications, disclose benzofused lactams which are disclosed as being useful in promoting release of growth hormone:

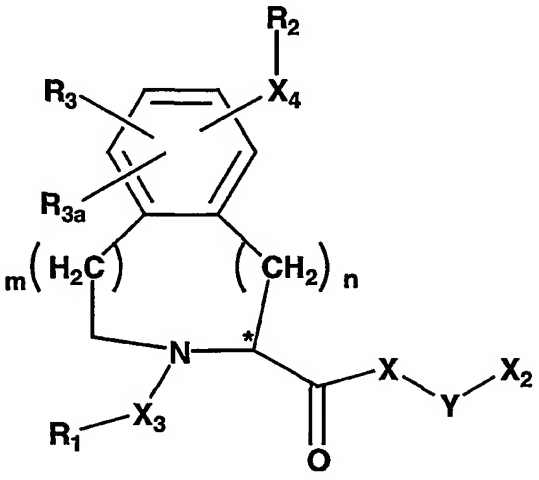
U.S. Patent Nos. 5,206,235; 5,283,741; 5,284,841; 5,310,737; 5,317,017; 5,374,721; 5,430,144; 5,434,261; 5,438,136; 5,545,735; 5,583,130; 5,606,054; 5,672,596 and 5,726,307; WO 96-05195 and WO 95-16675.

The following patents/applications disclose diverse chemotypes as being useful in promoting release of growth hormone:

U.S. Patent Nos. 5,536,716; 5,578,593; 5,622,973; 5,652,235; 5,663,171; WO 94-19367; WO 96-22997; WO 97-24369, WO 98-58948 and WO 00-10975.

Summary of the Invention

In accordance with the present invention, novel tetrahydroisoquinoline analogs are provided which are growth hormone secretagogues and have the structure I



wherein R_1 is alkyl, aryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkyl-alkoxy, alkoxyalkyl, alkylthioalkyl, aryloxyalkyl, arylalkoxyalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl, or heteroarylalkyl, and where these groups may be optionally substituted with 1 to 3 J1 groups which may be the same or different and the R_1 aryls may be further optionally substituted with 1 to 5 halogens, aryl, $-CF_3$, $-OCF_3$, 1-3 hydroxyls, 2 of which substituents where possible, may be joined by a methylene bridge;

R_2 is H, alkyl, aryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, aryloxyalkyl, arylalkoxyalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkylalkoxy, heteroaryl, or heteroarylalkyl, and where these groups may be optionally substituted with a J1a group and the aryls may be further optionally substituted with 1 to 5 halogens, $-CF_3$, $-OCF_3$, or 1-3 hydroxyls;

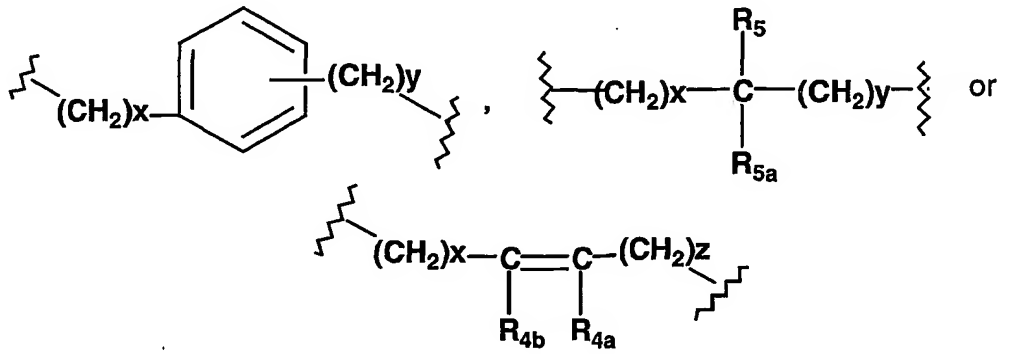
X is a bond, -O-, or -NR_4-;

R_3 and R_{3a} are the same or different and are independently selected from H, alkoxy, halogen, -CF_3, alkyl, or aryl;

R_4, R_{4a}, R_{4b}, R_{4c}, R_{4d}, R_{4e}, R_{4f}, R_{4g}, R_{4h}, R_{4i}, R_{4j}, R_{4k}, and R_{4l} are the same or different and are independently selected from H, C_1-C_6alkyl, or aryl;

m and n are the same or different and are independently 0 or 1;

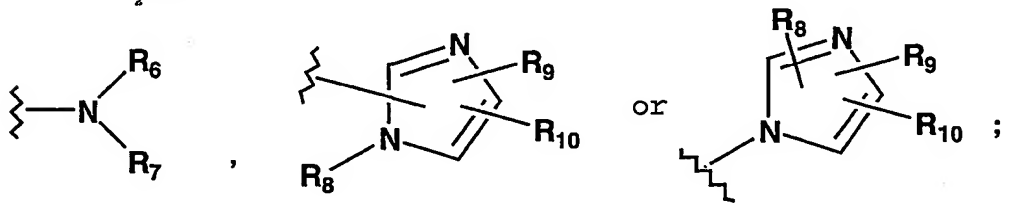
Y is



where x and y are the same or different and are independently 0 to 3 and z is 1 to 3;

R_5 and R_{5a} are the same or different and are independently H, alkyl, alkoxy, hydroxyl, halogen, -CF_3, aryl, alkaryl, and cycloalkyl; or R_5 and R_{5a} can be independently joined to one or both of R_6 and R_7 groups (see X_2) to form an alkylene bridge of 1 to 5 carbon atoms; or R_5 and R_{5a} can be joined together to form a ring of from 4-7 carbon atoms;

X_2 is



R_6 and R_7 are the same or different and are independently H or alkyl where the alkyl may be optionally substituted with halogen, 1 to 3 hydroxys, 1 to 3 C_1-C_{10}alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl,

phenoxy, or C_1-$_6$alkoxycarbonyl; or R_6 and R_7 can together form $-(CH_2)_tX_5(CH_2)_u-$ where X_5 is $-C(R_{4c})(R_{4d})-$, $-O-$ or $-N(R_{4e})-$, t and u are the same or different and are independently 1-3;

R_8 is H, C_1-C_6alkyl, $-CF_3$, alkaryl, or aryl, and with the alkyl and aryl groups being optionally substituted with 1 to 3 hydroxys, 1 to 3 C_1-C_{10}alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy or C_1-C_6alkoxycarbonyl;

R_9 and R_{10} are the same or different and are independently H, C_1-C_6alkyl, $-CF_3$, alkaryl, aryl, or halogen, and with the alkyl and aryl groups being optionally substituted with 1 to 3 hydroxys, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-$_6$ alkoxy, phenyl, phenoxy or C_1-C_6 alkoxycarbonyl;

X_3 is a bond, $-C(O)-$, $-C(O)O-$, $-C(O)N(R_{4f})-$, $-S(O)_2-$, or $-S(O)_2N(R_{4f})-$;

X_4 is a bond, $-O-$, $-OC(O)-$, $-N(R_{4g})-$, $-N(R_{4g})C(O)-$, $-N(R_{4g})C(O)N(R_{4h})-$, $-N(R_{4g})S(O)_2-$, $-N(R_{4g})S(O)_2N(R_{4h})$, $-OC(O)N(R_{4g})-$, $-C(O)-$, $-C(O)N(R_{4g})-$, $-S-$, $-S(O)_2-$, or $-S(O)_2N(R_{4g})-$;

J1 and J1a are the same or different and are independently nitro, halogen, hydroxyl, $-OCF_3$, $-CF_3$, alkyl, $-(CH_2)_vCN$, $-(CH_2)_vN(T_{1a})C(O)T_1$, $-(CH_2)_vN(T_{1a})C(O)OT_1$, $-(CH_2)_vN(T_{1a})C(O)N(T_{1a})T_1$, $-(CH_2)_vNT_1(T_{1a})$, $-(CH_2)_vN(T_{1a})SO_2T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOC(O)OT_1$, $-(CH_2)_vOC(O)T_1$, $-(CH_2)_vOC(O)OT_1$, $-(CH_2)_vOC(O)T_1$, $-(CH_2)_vOC(O)N(T_{1a})T_1$, $-(CH_2)_vN(T_{1a})SO_2N(T_{1b})T_1$, $-(CH_2)_vOT_1$, $-(CH_2)_vSO_2T_1$, $-(CH_2)_vSO_2N(T_{1a})T_1$, $-(CH_2)_vC(O)T_1$, $-(CH_2)_vCH(OH)T_1$, or heteroaryl as defined below, with v being 0-3;

T_1, T_{1a} and T_{1b} are the same or different and are independently H, alkyl, alkenyl, alkynyl, lower alkythioalkyl, alkoxyalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, or cycloalkyl, each of which may be optionally substituted with halogen, hydroxyl, $-C(O)NR_{4i}R_{4j}$, $-NR_{4i}C(O)R_{4j}$, $-CN$, $-N(R_{4i})SO_2R_{11}$,

-OC(O)R4i, -SO2 NR4iR4j, -SOR11, -SO2R11, alkoxy, -COOH, cycloheteroalkyl, or -C(O)OR11; with the proviso that T_1 cannot be hydrogen when it is connected to sulfur, as in SO_2T_1; or T_1 and T_{1a} or T_1 and T_{1b} can together form $-(CH_2)_rX_{5a}(CH_2)_s-$ where X_{5a} is $-C(R_{4k})(R_{41})-$, -O- or $-N(R_{4k})-$, r and s are the same or different and are independently 1-3;

R_{11} is C_1-C_6alkyl or aryl;

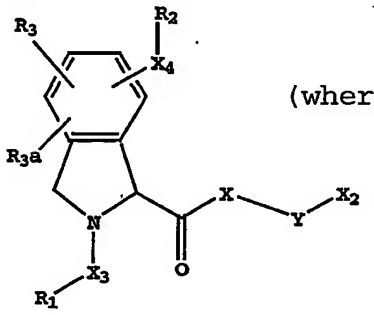
or a pharmaceutically acceptable salt thereof, or a prodrug ester thereof, and including all stereoisomers thereof;

(1) with the proviso that where m is O and n is 1, the moiety $-X_4-R_2$ is other than alkyl or alkoxy and

(2) where X is a bond and X_2 is amino, then m is 1.

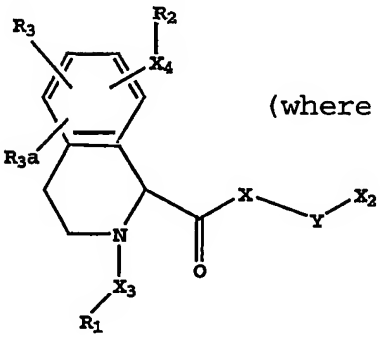
Thus, the compounds of formula I of the invention include compounds of the following structures.

IA



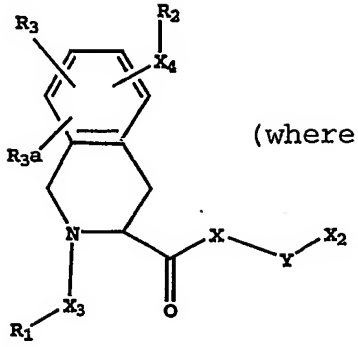
(where m is 0 and n is 0)

IB



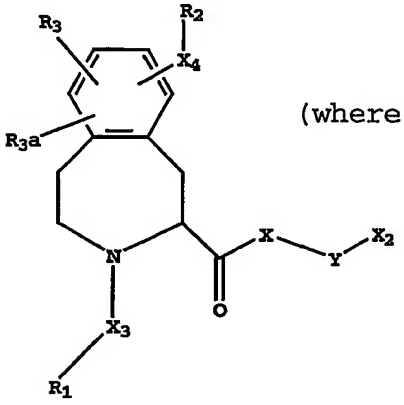
(where m is 1 and n is o)

IC



(where m is 0 and n is 1)

ID



(where m is 1 and n is 1)

The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in structural formula I. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof, be included within the ambit of the instant invention. The racemic mixtures may be separated into individual optical isomers employing conventional procedures such as by chromatography or fractional

crystallization. In the case of the asymmetric center represented by the asterisk in formula I, it has been found that compounds with either the R or S configuration are of almost equal activity. Therefore one isomer might be only slightly preferred, therefore both are claimed.

The pharmaceutically acceptable salts of the compounds of formula I of the invention include alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium, as well as zinc or aluminum and other cations such as ammonium, choline, diethanolamine, ethylenediamine, t-butylamine, t-octylamine, dehydroabietylamine, as well as pharmaceutically acceptable anions such as chloride, bromide, iodide, tartrate, acetate, methanesulfonate, maleate, succinate, glutarate, and salts of naturally occurring amino acids such as arginine, lysine, alanine and the like, and prodrug esters thereof.

In addition, in accordance with the present invention, a method for increasing levels of endogenous growth hormone or increasing the endogenous production or release of growth hormone is provided wherein a compound of formula I as defined hereinbefore is administered in a therapeutically effective amount.

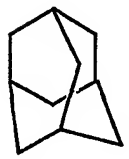
Furthermore, in accordance with the present invention, a method is provided for preventing or treating osteoporosis (improving bone density and/or strength), or treating obesity, or increasing muscle mass and/or muscle strength, or maintenance of muscle strength and function in elderly humans, or reversal or prevention of frailty in elderly humans, wherein a compound of formula I as defined hereinbefore is administered in a therapeutically effective amount.

Detailed Description of the Invention

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 40 carbons, preferably 1 to 20 carbons, more preferably 1 to 6 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 3 substituents including alkyl, aryl, alkenyl, alkynyl, hydroxy, arylalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, arylalkyloxy, alkanoyl, amino, haloaryl, CF_3, OCF_3, aryloxy, heteroaryl, cycloalkylalkoxyalkyl, or cycloheteroalkyl.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 3 to 7 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, cyclohexenyl,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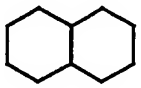
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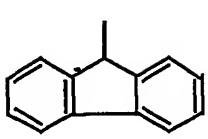
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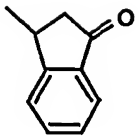
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any of which groups may be optionally substituted with 1 to 3 substituents as defined above for alkyl.

The term "aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl) and may optionally include one to three additional rings fused to "aryl" (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings) and may be optionally substituted through available carbon atoms with 1 to 5 halo, 1, 2, or 3 groups selected from hydrogen, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkylalkyl, fluorenyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, oxo, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl, or preferably any of the aryl substituents as set out above.

Preferred aryl groups include phenyl, biphenyl or naphthyl.

The term "aralkyl", "aryl-alkyl" or "aryllower alkyl" as used herein alone or as part of another group refers to alkyl groups as discussed above having an aryl

substituent, such as benzyl or phenethyl, or naphthylpropyl, or an aryl as defined above.

The term "lower alkoxyl", "alkoxyl", "aryloxyl" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

The term "amino" as employed herein alone or as part of another group may optionally be substituted with one or two substituents such as alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and/or cycloalkyl.

The term "lower alkylthio", alkylthio", "alkylthioalkyl", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

The term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

The term "acyl" as employed herein by itself or part of another group, as defined herein, refers to an organic radical linked to a carbonyl $\left(\overset{O}{\overset{\|}{C}}\right)$ group; examples of acyl groups include alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl, and the like.

The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 3 to 12 carbons, and more preferably 2 to 6 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl,

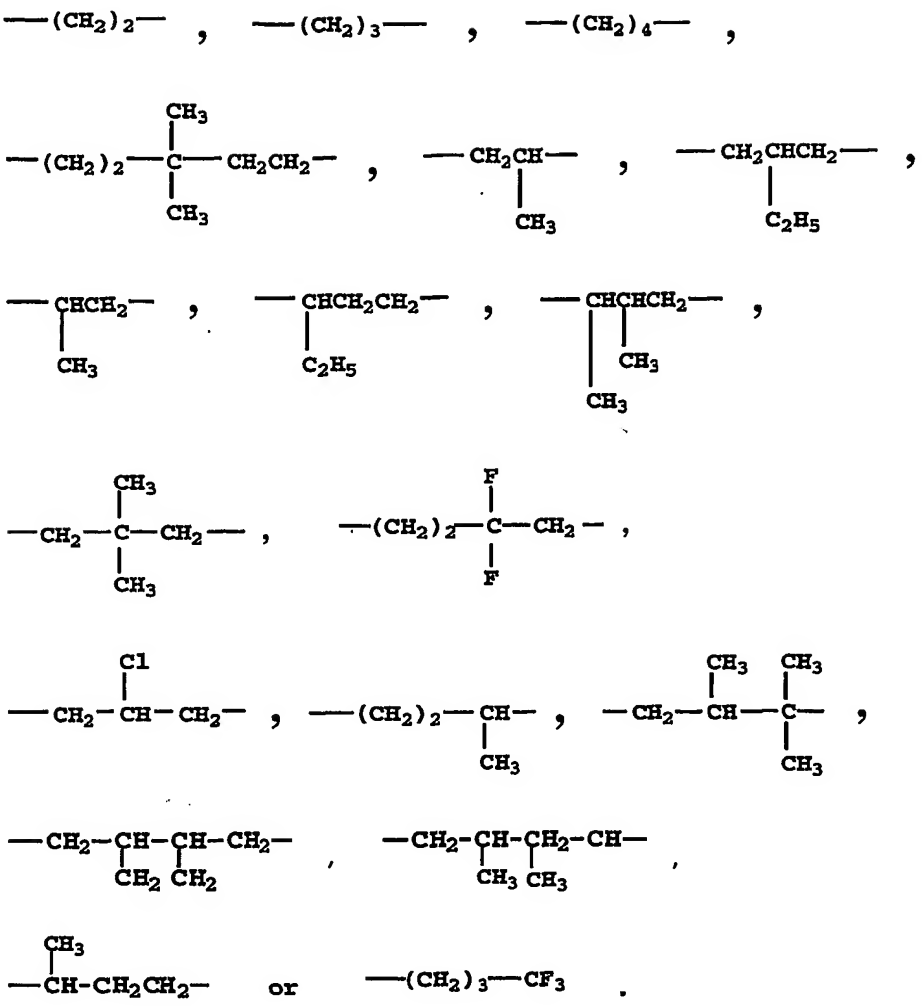
4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, alkylthio or any of the substituents for alkyl as set out herein.

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, or any of the substituents for alkyl as set out herein.

The term "alkylene" as employed herein alone or as part of another group refers to alkyl groups as defined above having single bonds for attachment to other groups at two different carbon atoms and may optionally be substituted as defined above for "alkyl".

The terms "alkenylene" and "alkynylene" as employed herein alone or as part of another group refer to alkenyl groups as defined above and alkynyl groups as defined above, respectively, having single bonds for attachment at two different carbon atoms.

Examples of $(CH_2)_m$, $(CH_2)_n$, $(CH_2)_p$, $(CH_2)_r$, $(CH_2)_s$, $(CH_2)_t$, $CH_2)_u$, $(CH_2)_v$, $(CH_2)_x$, $(CH_2)_y$, $(CH_2)_z$, and other groups (which may include alkylene, alkenylene or alkynylene groups as defined herein, and may optionally include 1, 2, or 3 substituents which may be any of the substituents for alkyl set out herein), are as follows:



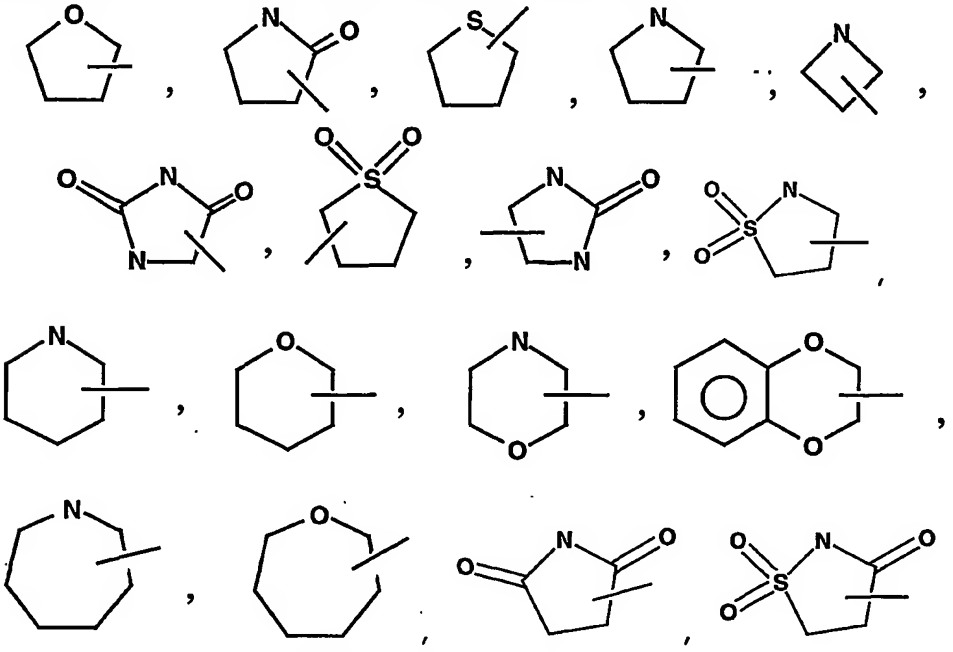
The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF_3, with chlorine or fluorine being preferred.

The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

The term "heterocyclic", "heterocyclo" or "heterocycle" as employed herein alone or as part of another group refers to "heteroaryl" groups or "cycloheteroalkyl" groups.

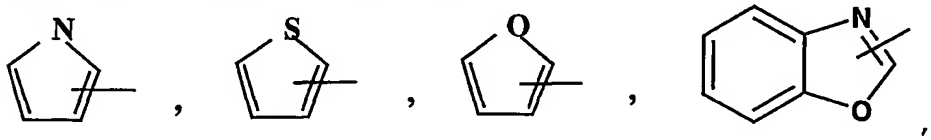
The term "cycloheteroalkyl" as used herein alone or as part of another group refers to a 4-, 5-, 6- or 7-

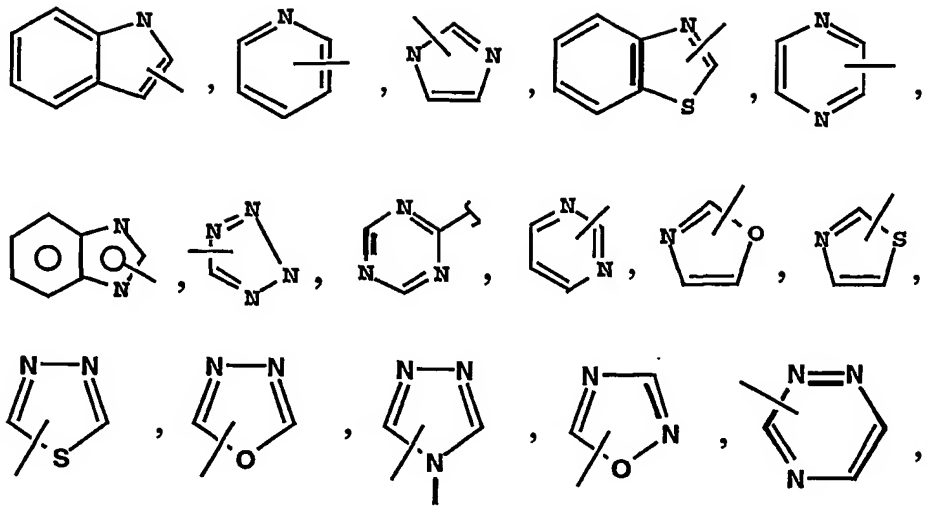
membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (which is defined above), such as



and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, oxo and/or any of of the aryl substituents set out herein. In addition, any of the above rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

The term "heteroaryl" as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur,and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), and includes possible N-oxides, such as





and the like.

The heteroaryl groups may optionally include 1 to 4 substituents such as any of the aryl substituents set out herein as well as carbonyl and arylcarbonyl. In addition, any of the above rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

Preferred are compounds of formula IB wherein R_1 is alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, aryloxyalkyl, heteroaryl, or heteroarylalkyl, and where these groups may be further optionally substituted with a J1 group;

R_2 is alkyl, aryl, arylalkyl, alkoxyalkyl, aryloxyalkyl, heteroaryl, cycloalkyl, cycloalkylalkyl, or heteroarylalkyl, and these groups may be further optionally substituted by J1a;

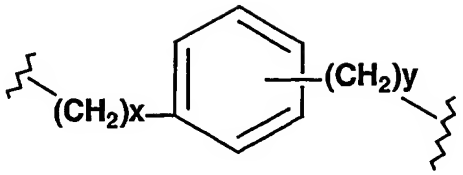
X is -O- or $-N-R_4$;

R_3 and R_{3a} are the same or different and are independently H, alkoxy, halogen, -CF3;

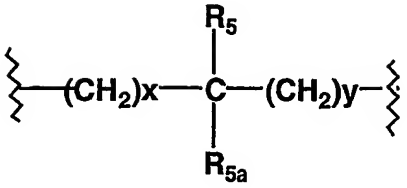
R_4 is H or C_1-C_6 alkyl;

m and n are independently 0 or 1;

Y is



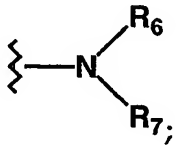
or



where x and y are independently 0 to 3;

R_5 and R_{5a} are the same or different and are independently H, alkyl, $-CF_3$, or R_5 and R_{5a} can be independently joined to one or both of R_6 and R_7 groups (see X_2) to form an alkylene bridge of 1 to 5 carbon atoms;

X_2 is



R_6 and R_7 are the same or different and are independently H or alkyl, where alkyl can optionally be substituted with halogen, 1 or 2 hydroxyls, 1 or 2 C_1-C_{10} alkanoyloxy, 1 or 2 C_1-C_6 alkoxy, phenyl, phenoxy, C_1-C_6 alkoxycarbonyl; or R_6 and R_7 can together form $-(CH_2)_tX_5(CH_2)_u-$ where X_5 is $C(R_4)(R_{4a})$ or O, t and u are independently 1-3;

X_3 is $-C(O)-$, $-C(O)O-$, or $-S(O)_2N(R_4)$;

X_4 is a bond, $-O-$, $-OC(O)-$, or $-N(R_4)C(O)-$;

J1 is $-(CH_2)_vCN$, $-(CH_2)_vN(T_{1a})C(O)T_1$, $-(CH_2)_vN(T_{1a})C(O)OT_1$, $-(CH_2)_vN(T_{1a})C(O)N(T_{1b})T_1$, $-(CH_2)_vSO_2T_1$, $-(CH_2)_vN(T_{1a})SO_2T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOC(O)T_1$, $-(CH_2)_vOC(O)N(T_{1a})T_1$, $-(CH_2)_vN(T_{1a})SO_2N(T_{1b})T_1$, $-(CH_2)_vOT_1$, $-(CH_2)_vSO_2N(T_{1a})T_1$, $-(CH_2)_vC(O)T_1$, or heteroaryl, with v being 0-2;

J1a is halogen, $-(CH_2)_vCN$, $-(CH_2)_vN(T_{1a})C(O)T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOT_1$, or $-(CH_2)_vC(O)T_1$, with v being 0-2;

T_1, T_{1a} and T_{1b} are the same or different and are independently H, alkyl, aryl, alkaryl, or cycloalkyl;

each optionally substituted with halogen, hydroxyl or alkoxy; with the proviso that T_1 cannot be hydrogen when it is connected to sulfur as in SO_2T_1;

Most preferred are compounds of the formula IB, wherein R_1 is alkyl, aryl, arylakyl, cycloalkyl, and cycloalkylalkyl and where these groups may be further optionally substituted with a J1 group;

R_2 is alkyl, aryl, arylalkyl, or cycloalkyl, and these groups may be further optionally substituted by J1a;

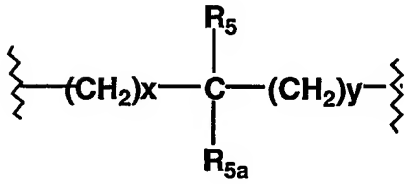
X is -NH or $-NCH_3$;

R_3 and R_{3a} are each H;

m is 1;

n is 0;

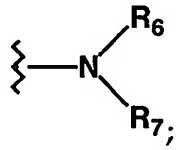
Y is



where x and y are independently 0 or 1, with the proviso that both cannot be 0;

R_5 and R_{5a} are the same or different and are independently H, alkyl, $-CF_3$; or R_5 and R_{5a} can be independently joined to one or both of R_6 and R_7 groups (see X_2) to form an alkylene bridge of 1 to 5 carbon atoms;

X_2 is



R_6 and R_7 are the same or different and are independently H or alkyl where alkyl may be optionally substituted with halogen, or 1 to 2 hydroxyls;

X_3 is $-C(O)-$, $-C(O)O-$, or $-S(O)_2N(R_{4E})$;

X_4 is $-O-$, or $-OC(O)-$;

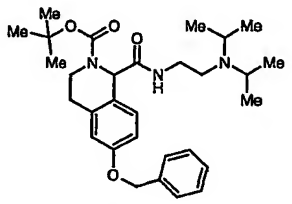
J1 is $-(CH_2)vCN$, $-(CH_2)vN(T_{1a})C(O)T_1$,

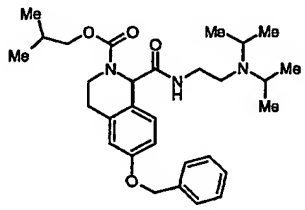
$-(CH_2)_vN(T_{1a})C(O)OT_1$, $-(CH_2)_vN(T_{1a})C(O)N(T_{1b})T_1$, $-(CH_2)_vSO_2T_1$, $-(CH_2)_vN(T_{1a})SO_2T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOC(O)T_1$, $-(CH_2)_vOC(O)N(T_{1a})T1$, $-(CH_2)_vN(T_{1a})SO_2N(T_{1b})T_1$, $-(CH_2)_vOT_1$, $-(CH_2)_vSO_2N(T_{1a})T_1$, $-(CH_2)_vC(O)T_1$, or heteroaryl, with v being 0-2;

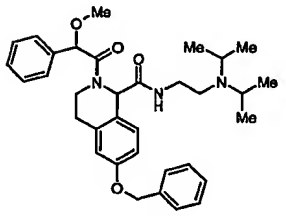
J1a is halogen, $-(CH_2)_vCN$, $-(CH_2)_vN(T_{1a})C(O)T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOT_1$, or $-(CH_2)_vC(O)T_1$, with v being 0-2;

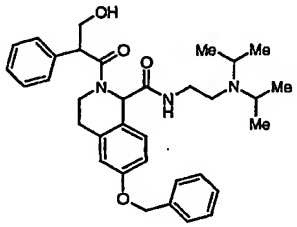
T_1, T_{1a} and T_{1b} are the same or different and are independently H, alkyl, aryl or alkaryl, each optionally substituted with halogen, hydroxyl or alkoxy; with the proviso that T_1 cannot be hydrogen when it is connected to carbonyl or sulfur, as in $C(O)T_1$ or SO_2T_1;

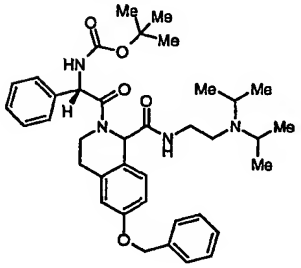
Examples of preferred compounds of the invention include the following:

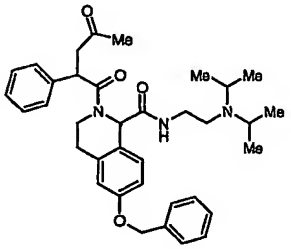


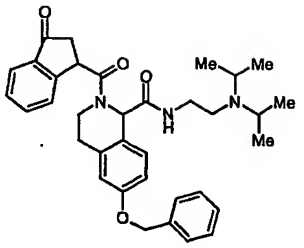


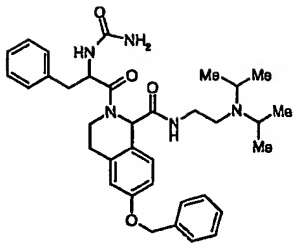


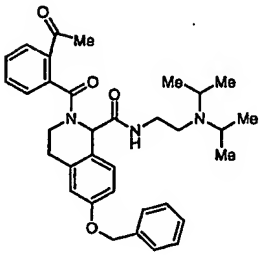


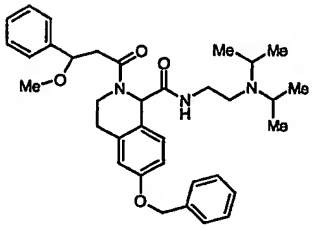


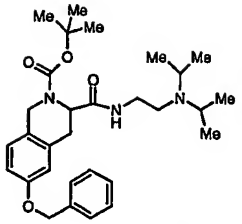


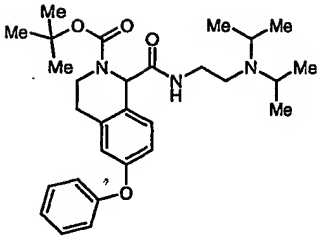


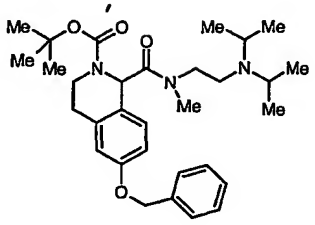












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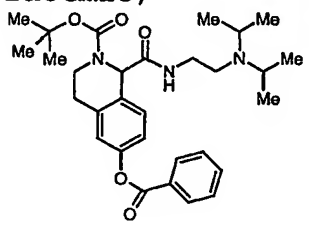
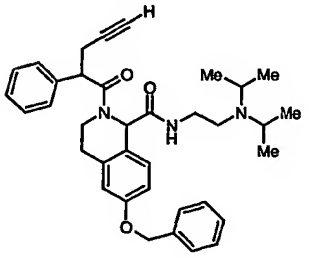
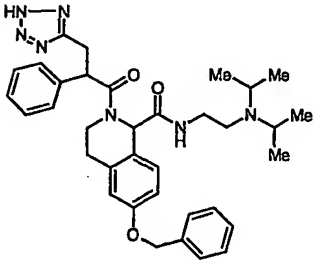
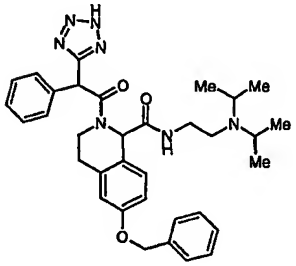
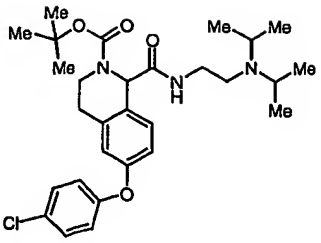
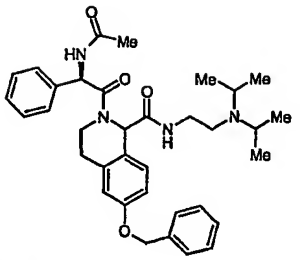


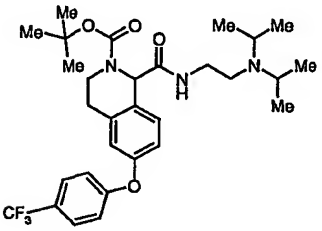


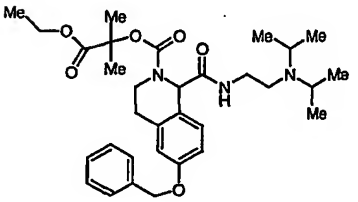


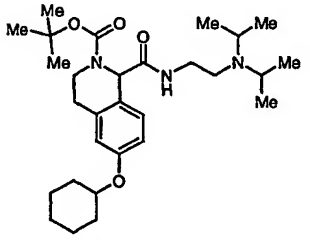


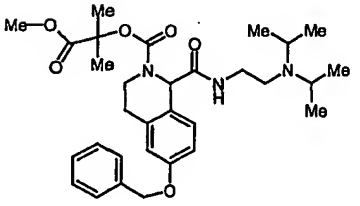


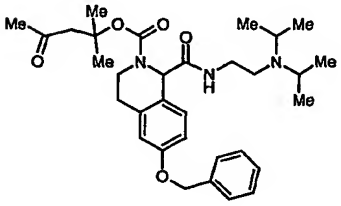


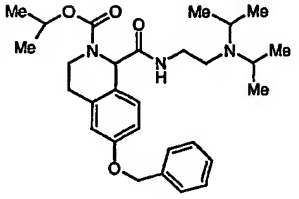


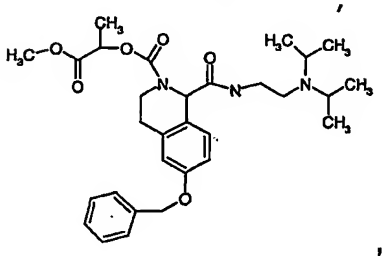


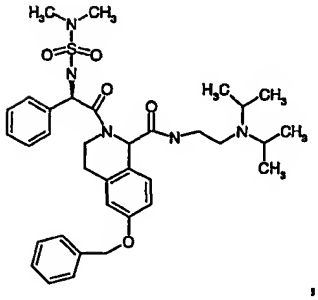




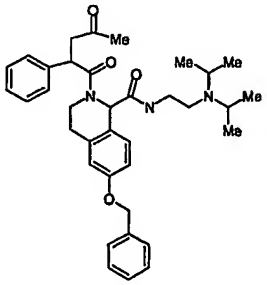




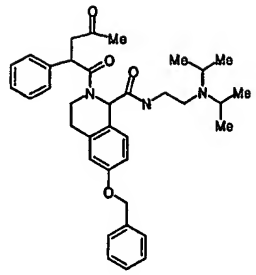


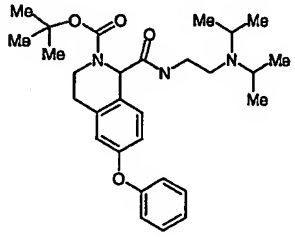


Diastereomer A

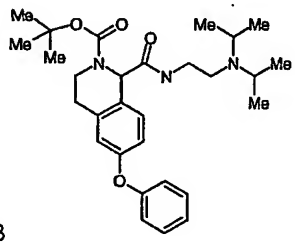


Diastereomer A

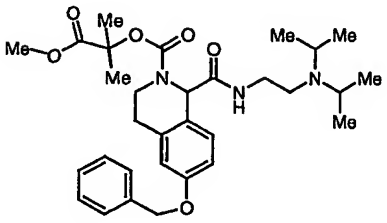


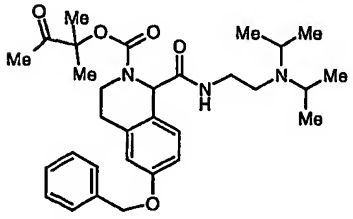


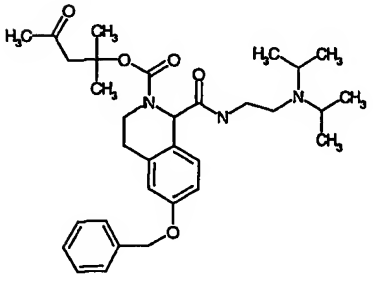
Isomer A

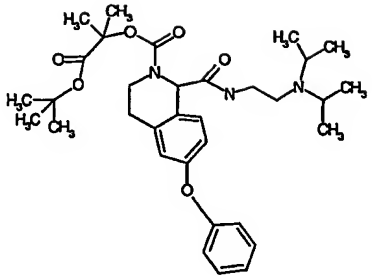


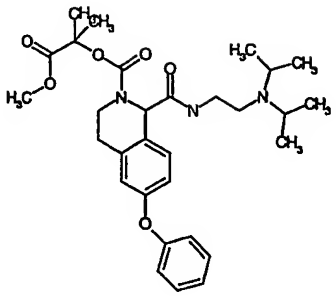
Isomer B



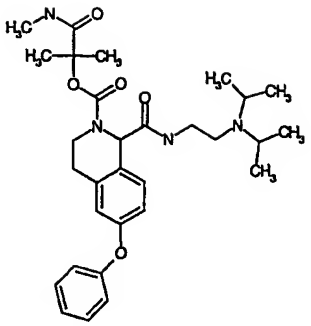








Isomer A,



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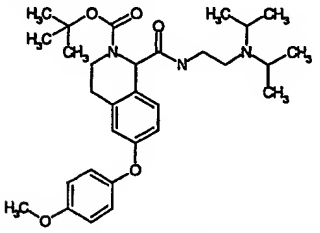

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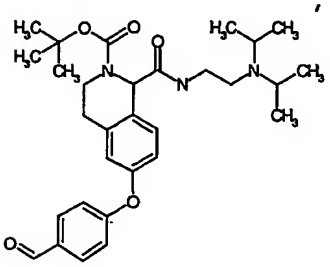

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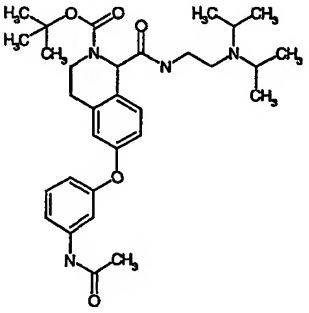

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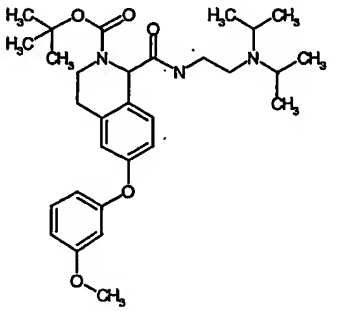

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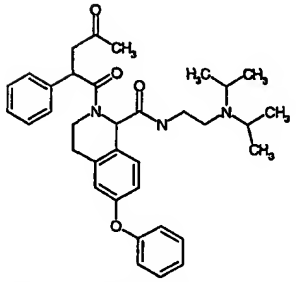

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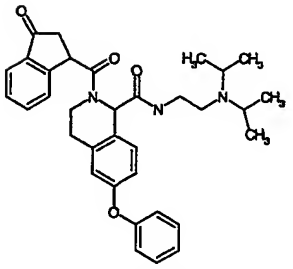

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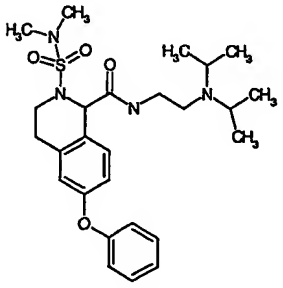
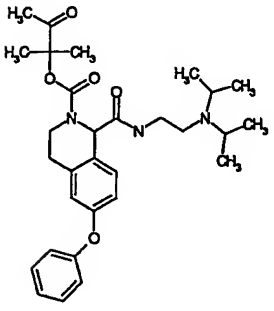


Isomer A,



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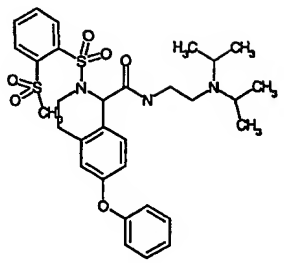
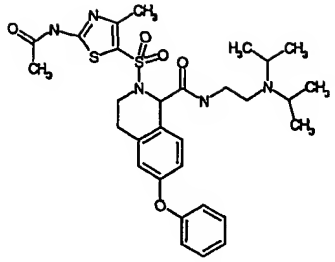
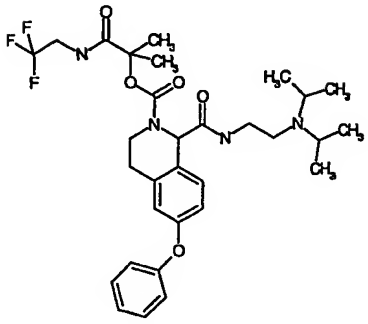
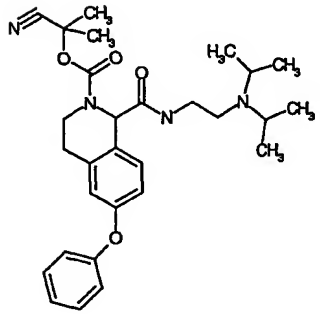
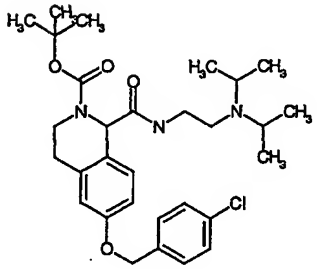
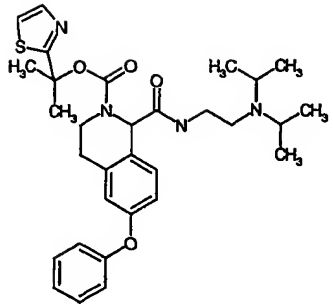


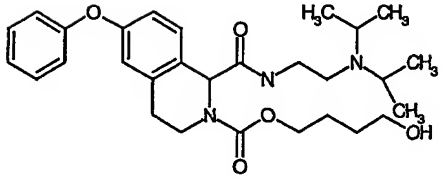


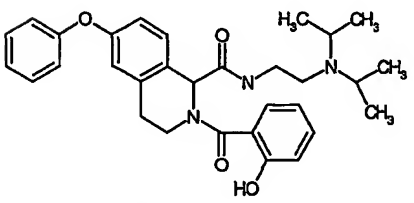


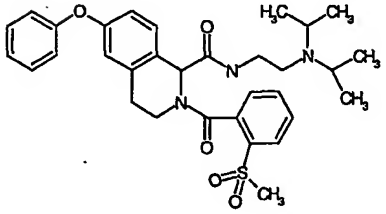


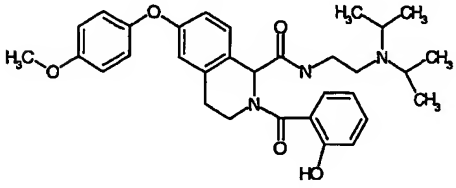


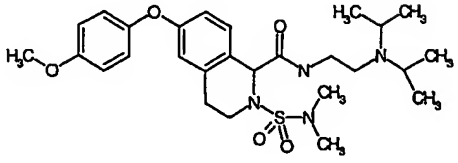












General Synthetic Schemes

The compounds of the present invention may be prepared according to the following general synthetic schemes, as well as relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples. Unless otherwise specified, the various substituents of the compounds are defined in the same manner as the formula I compound of the invention.

With respect to the following reaction schemes, amide bond forming reactions are conducted under standard peptide coupling procedures know in the art. Optimally, the reaction is conducted in a solvent such as DMF at 0°C to room temperature using EDAC (WSC) (1-ethyl-3-(dimethyl- aminopropyl)carbodiimide), HOBt(1-hydroxybenzotriazole) or HOAt (1-hydroxy-7-aza-benzotriazole) and a base (Hunigs base). Carbamates of formula IE can be formed under standard conditions known in the art from chloroformates, the piperidine amine and a base.

Tetrahydroisoquinolines can be formed as shown in Scheme 1. Suitable cyclization procedures are described in *J. Med. Chem.*, 87, 1821-1825 (1984), *Tet. Lett*, 21, 4819 (1980), *Synthesis*, 824 (1987). Alternative examples are shown in Scheme 8 (*J. Org. Chem.*, 61, 8103-8112 (1996); *Tetrahedron*, 43, 5095 (1987)), Scheme 9 (*Syn. Com.* 23, 473-486 (1993); *J Chem. Soc., Perkin Trans 1*, 2497 (1996); *Tet. Lett.*, 37, 5329 (1996)), and Scheme 10 (*Tetrahedron*, 50, 6193 (1994); *Tet. Lett.*, 34, 5747-5750 (1993); *J Chem Soc, Chem Commun*, 11, 966 (1993)) and Scheme 11. The intermediate A in Scheme 8 can be prepared by suitable methods known in the art, such as in *Tet. Lett*, 37, 5453 (1996) and *Synthesis*, 824 (1987). The protecting group Pc in Scheme 8 can be chiral (formamidine activation Meyers, A. I., *J. Org. Chem.*, 61,

8103-8112 (1990)), imparting chirality to compounds 48-50. The synthesis outlined in Scheme 10 can also lead to chiral induction in intermediates 66-71. Intermediates 49, 50, 61, 71 and 78 in Schemes 8 to 11 can be further transformed by methods disclosed in Schemes 1-7.

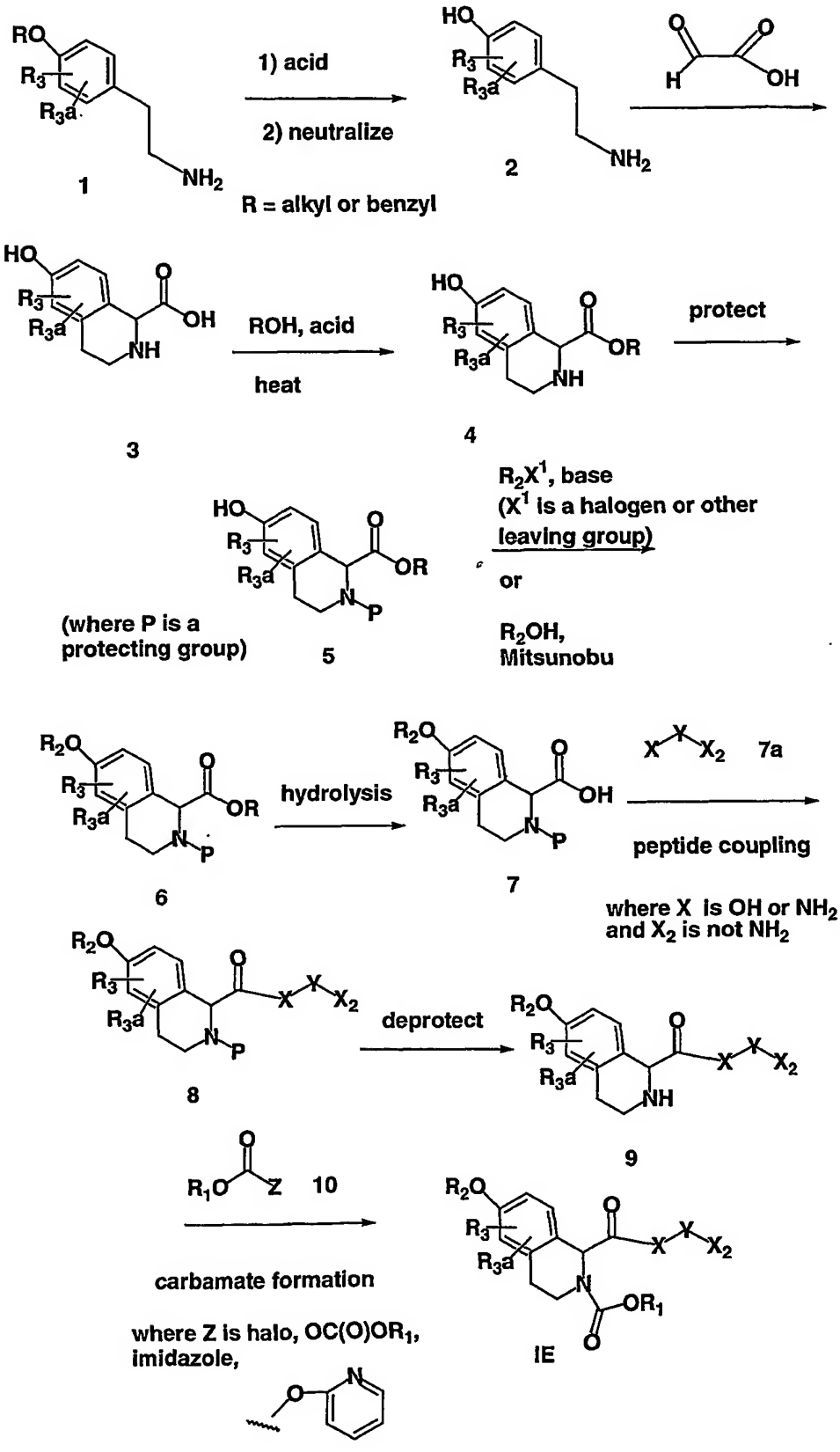
Protection and deprotection in the Schemes below may be carried out by procedures generally known in the art. See, for example, T. W. Greene, Protecting Groups in Organic Synthesis, Second Edition, 1991. P in the Schemes below denotes a nitrogen protecting group, optimally BOC or Cbz. The BOC group can be removed under acidic conditions, optimally HCl or trifluoroacetic acid. The Cbz group can be removed via hydrogenolysis, optimally using a palladium catalyst and hydrogen, or using TMSI. P1 in the Schemes below denotes a phenol protecting group such as BOC (removed by acid or base hydrolysis) or benzyl (removed by hydrogenolysis or TMSI).

Phenol intermediates shown in the General Schemes below may be acylated by methods known in the art to prepare esters and carbamates. The same phenol intermediates may be transformed into anilines by methods known in the art, such as Rossi, *J Org Chem*, 37 (1972). The anilines may be acylated by methods known in the art to prepare amides, ureas, and other derivatives covered by X4. The same phenol intermediates can be transformed to acids, esters or amides through an activated intermediate, such as triflate, by methods known in the art; phenol to acid: Jutand *J Chem Soc.*, 23, 1729-1730 (1992), Wang *Tet. Lett.*, 37, 6661-6664 (1996); to esters: Fretz *Tet. Lett.*, 37, 8475-8478 (1996), Horikawa *Heterocycles*, 40, 1009-1014 (1995) ; to amides: Cacchi *Tet. Lett.*, 27, 3931 (1986); to sulfides: Arould *Tet. Lett.*, 37, 4523-4524 (1996), Percec *J Org Chem*, 60, 6895-6903 (1995), Meier *Angew Chem*, 106, 493-495 (1994), Wong *J Med Chem*, 27, 20 (1984). The resulting sulfides can be oxidized to sulfones and sulfoxides by standard methods known in the art, such as meta-chloroperoxybenzoic acid.

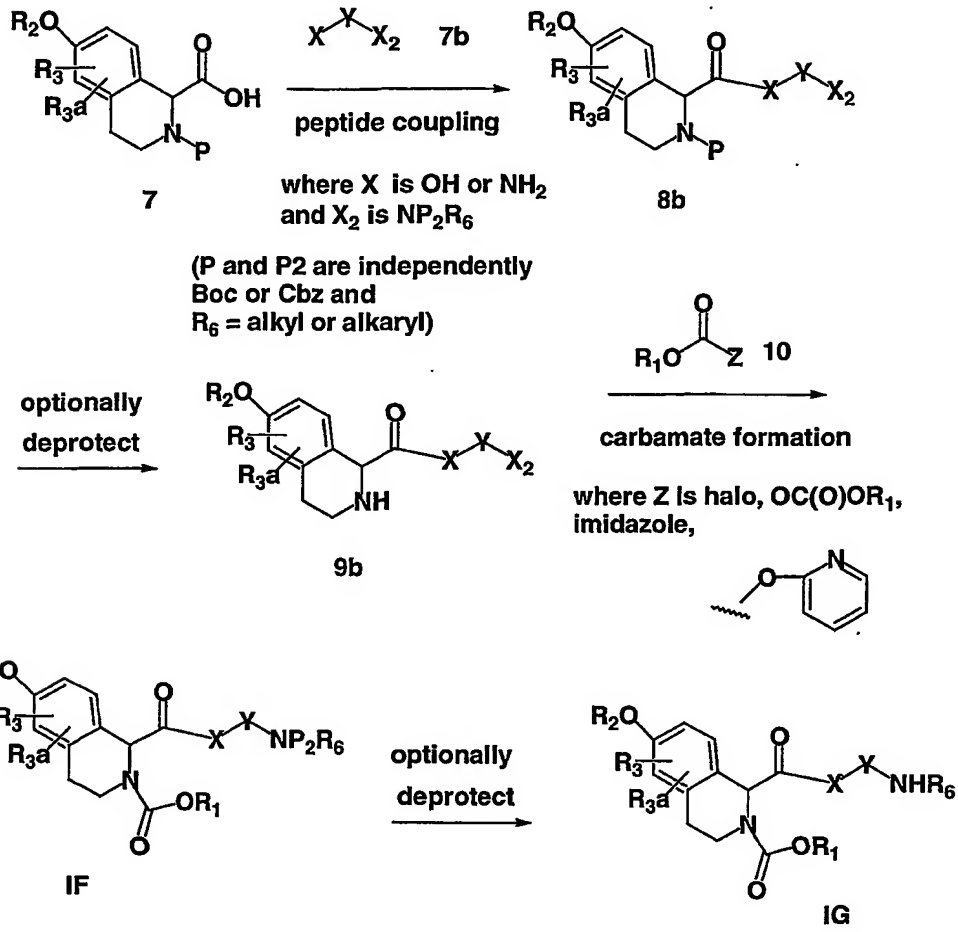
The arylation reaction covered in Scheme 2 can be performed under the coupling conditions in the literature described in Evans et al, *Tet Lett*, 39, 2937-2940 (1998).

Please note that in the following Schemes 1-10 the compounds of formula IB (m=1 and n=0) are shown. However, the schemes are also applicable in preparing all compounds of the formula I invention including compounds of formulae IA, IC and ID of the invention employing reagents or starting materials analogous to those shown in the schemes as will be apparent to one skilled in the art. In the following schemes R_2 is other than hydrogen.

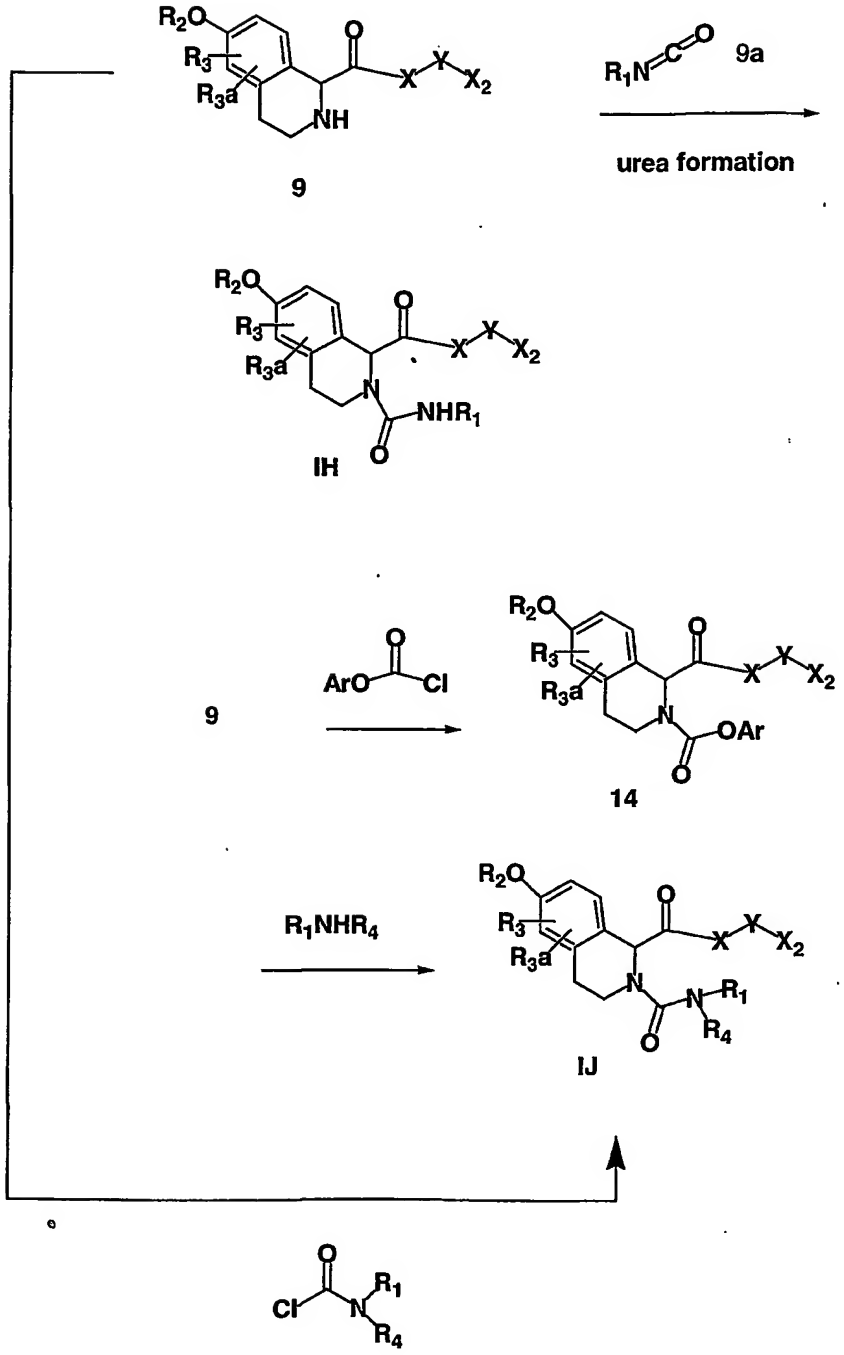
General Scheme 1: Carbamates



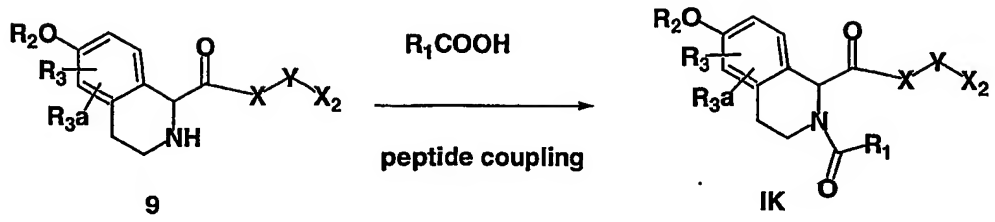
General Scheme 1 alternate: Carbamates



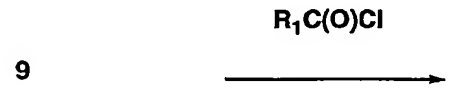
General Scheme 1a: Ureas



General Scheme 1b: Amides

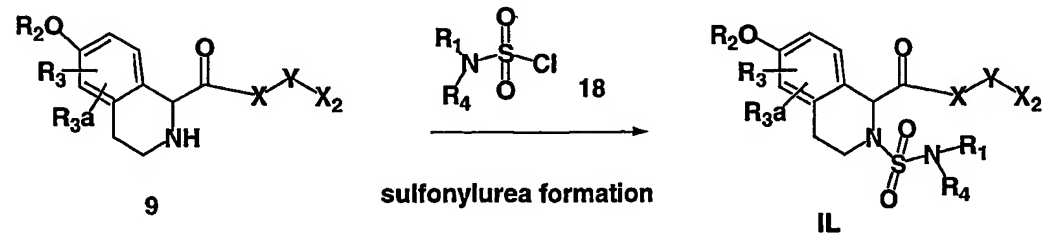


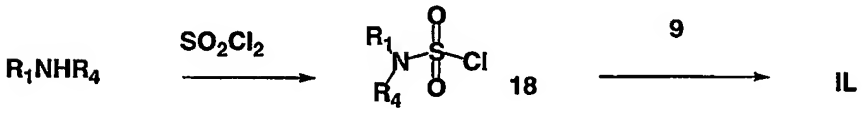
9 IK



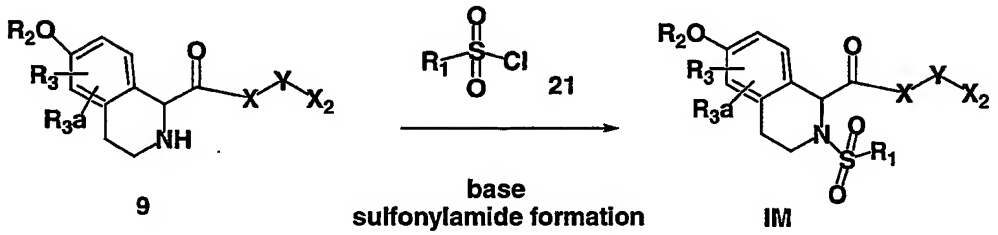
9 IK

General Scheme 1c: SulfonylUreas

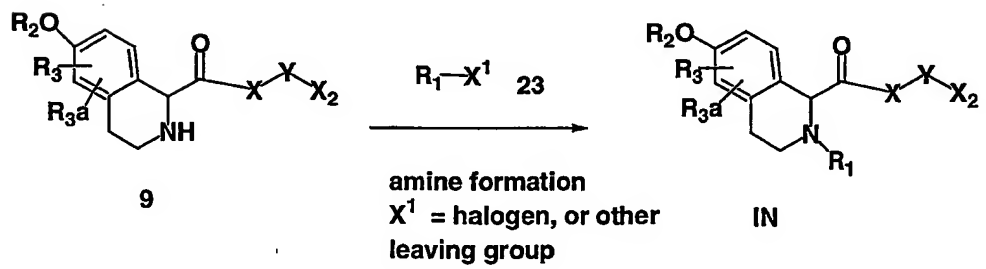




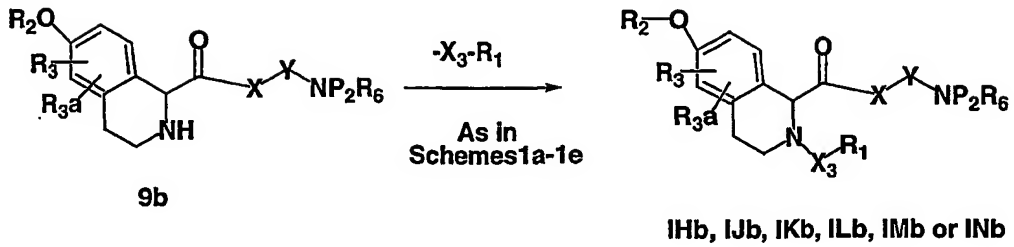
General Scheme 1d: Sulfonylamides



General Scheme 1e: Amines



General Scheme 1f

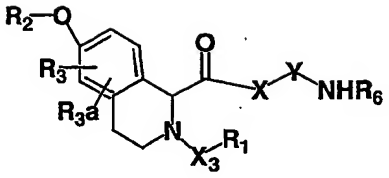


9b

IHb, IJb, IKb, ILb, IMb or INb

optionally deprotect

IHc, IJc, IKc, ILc, IMc or INc

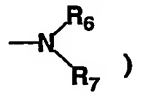


IHc, IJc, IKc, ILc
IMc or INc

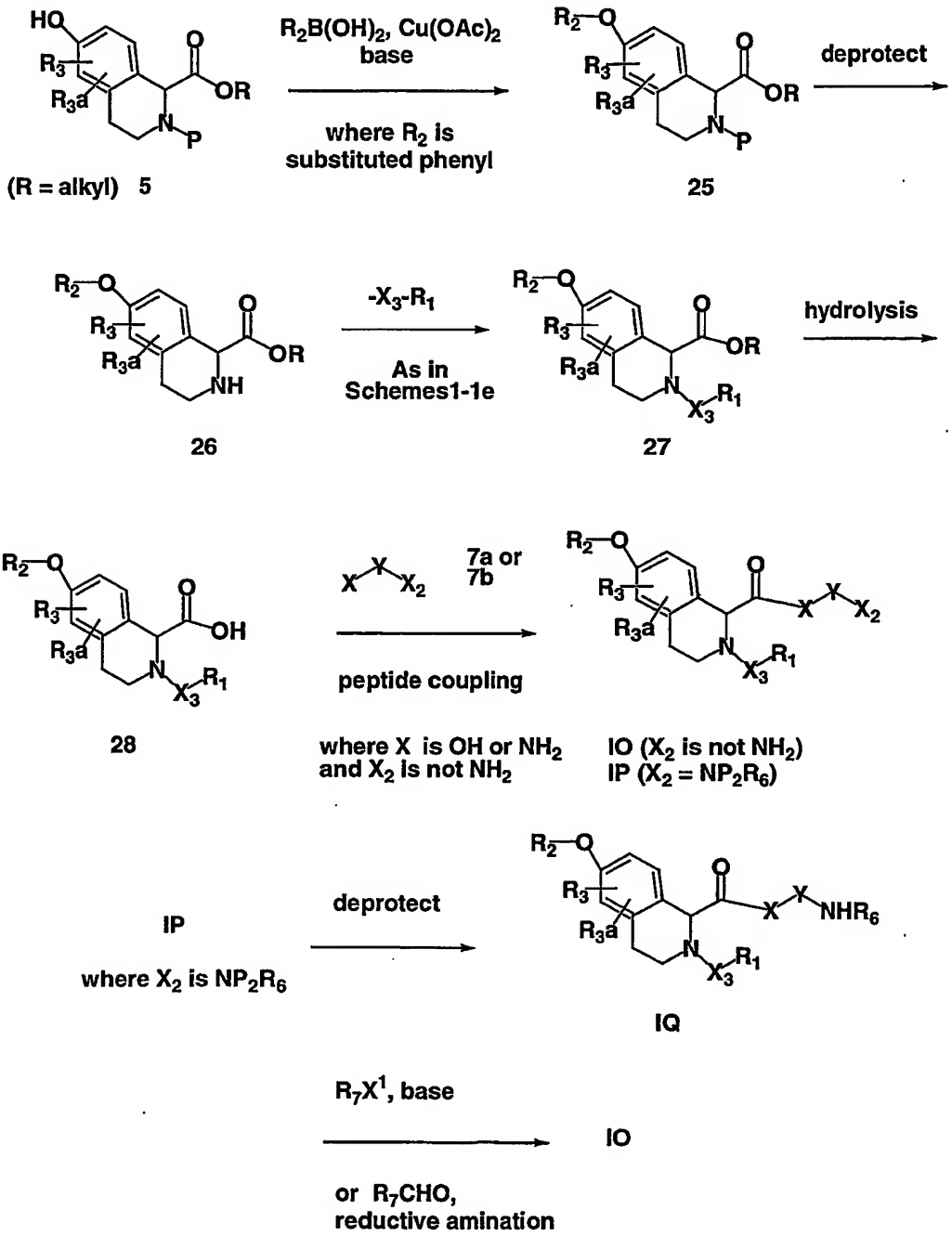
R_7X^1, base

or R_7CHO, reductive amination

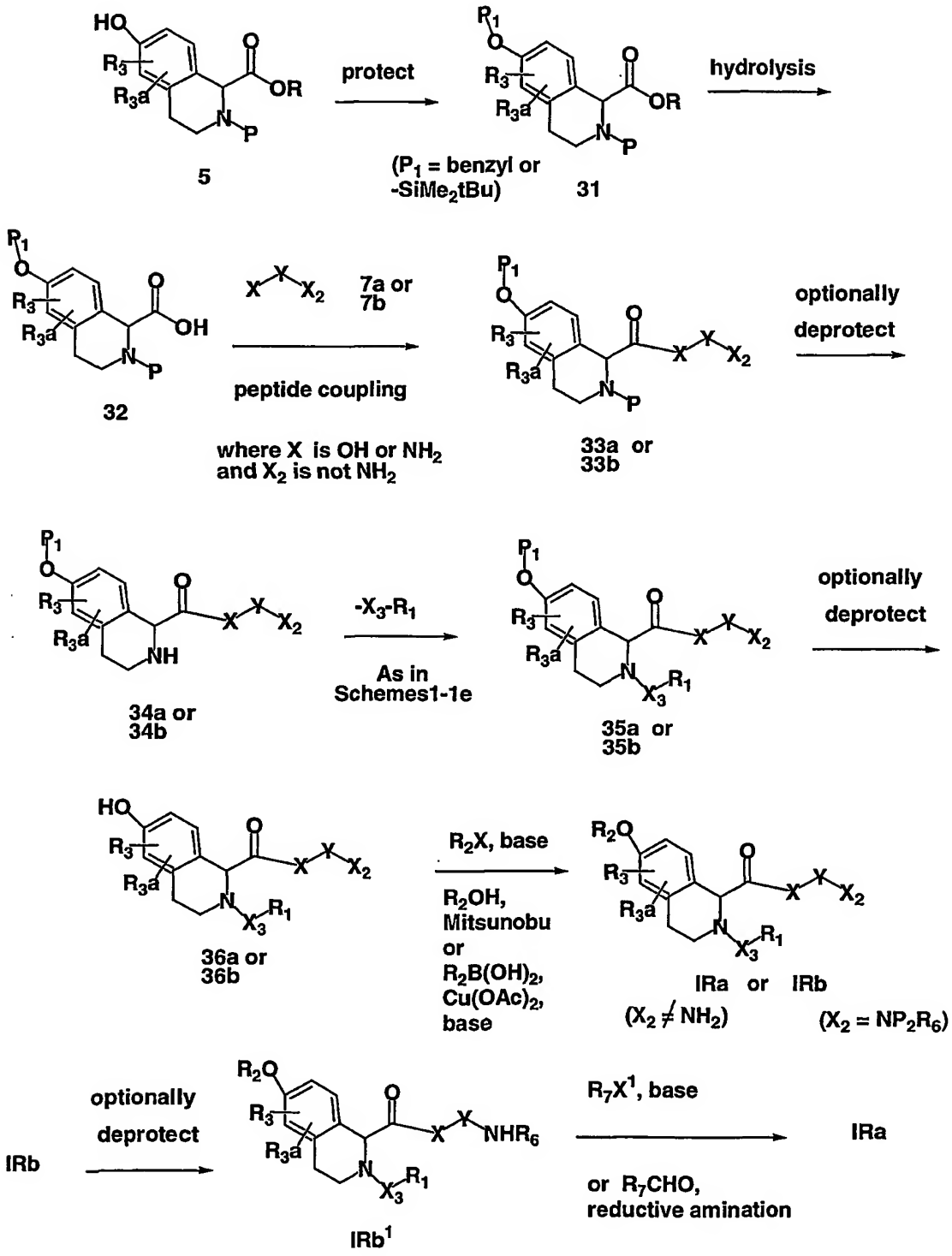
IH, IJ, IK, IL,
IM or IN

(where X_2 is )

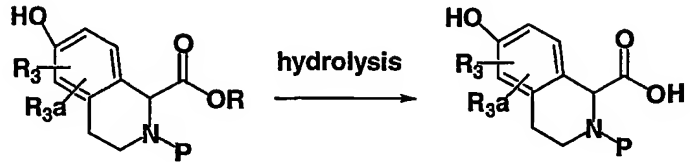
General Scheme 2: Arylation: Where R_2 is Phenyl



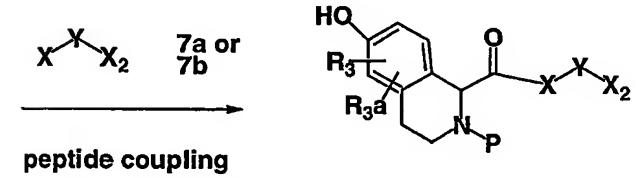
General Scheme 3



General Scheme 4: Alternate to 9 or 9b



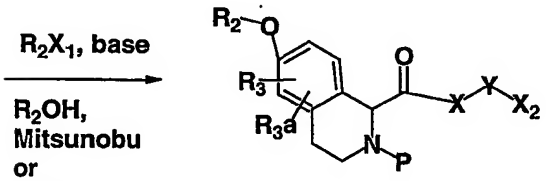
5 39



peptide coupling

where X is OH or NH_2
and X_2 is not NH_2

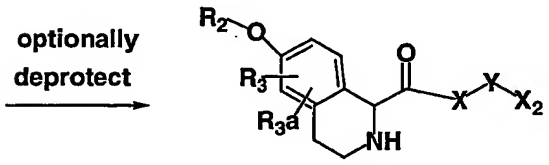
40a or
40b



R_2X_1, base

R_2OH,
Mitsunobu
or
$R_2B(OH)_2$,
$Cu(OAc)_2$,
base

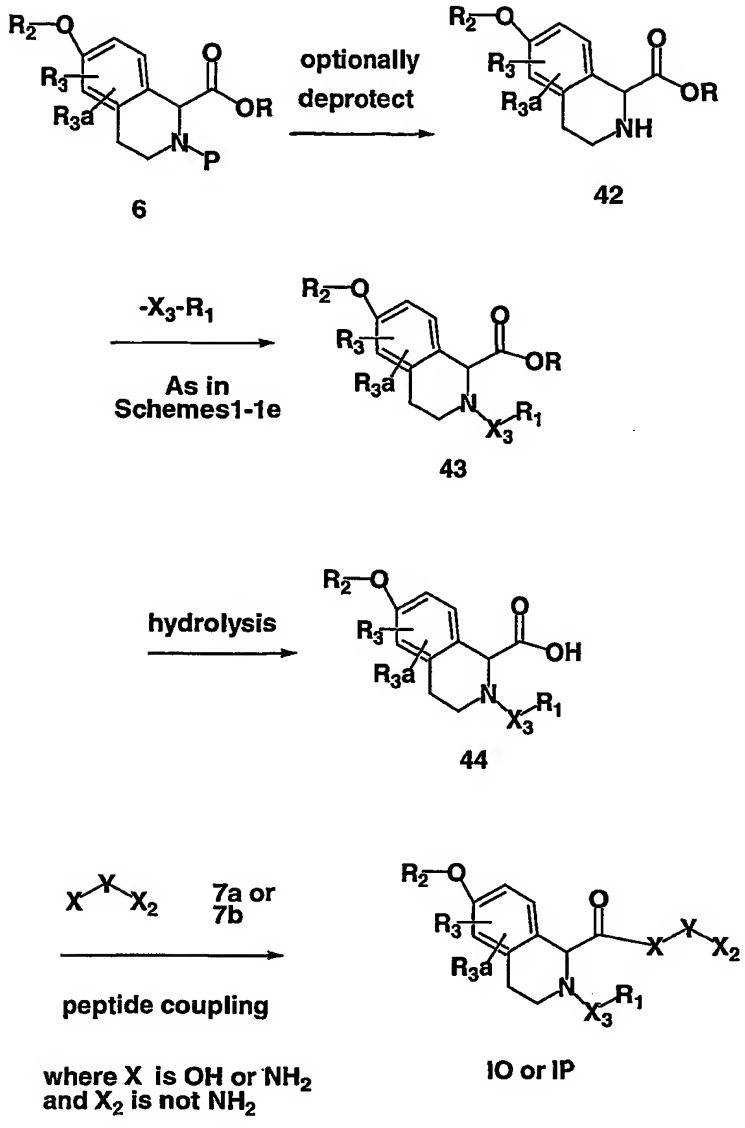
41 or
41b



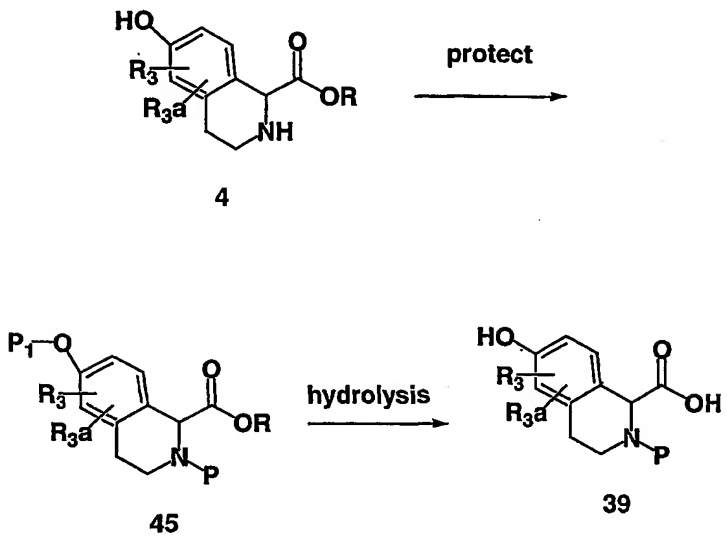
optionally
deprotect

9a or 9b

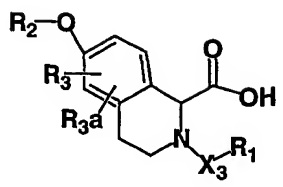
General Scheme 5



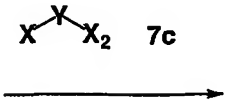
General Scheme 6: Intermediate 39



General Scheme 7



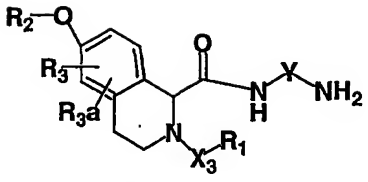
28 or 44



7c

peptide coupling

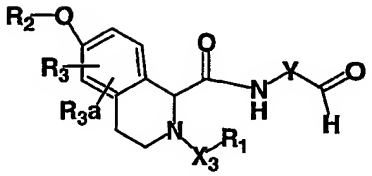
where X and X_2 are NH_2



46

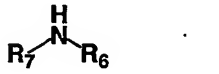
peptide coupling

28 or 44

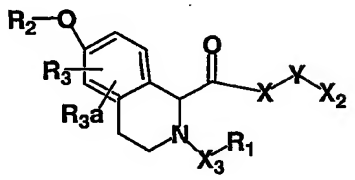


47

methods known
in the art
where X is -OH or $-NH_2$
and
W is an aldehyde or aldehyde precursor
(such as $-CH_2OH$ or $-CH(OMe)_2$)



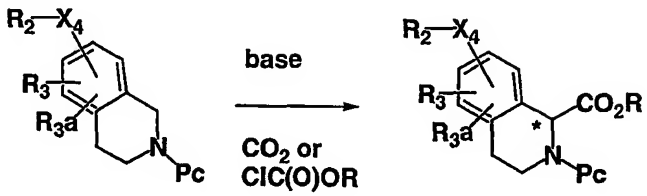
reductive amination



IO or IP

($X_2 \neq NH_2$)

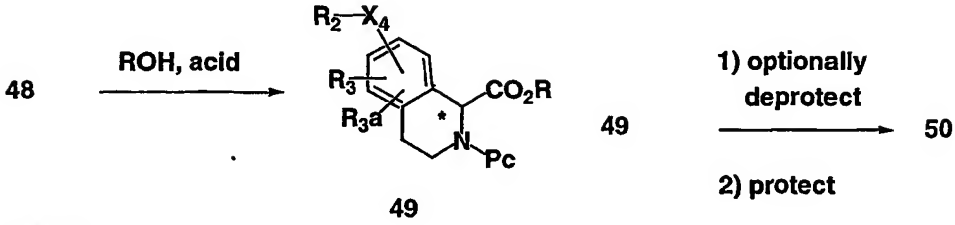
General Scheme 8: Alternate Routes to Core

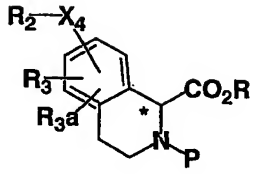


A

(Pc is a protecting group such as Boc or a chiral imine)

48: R = H
or
49: R = alkyl





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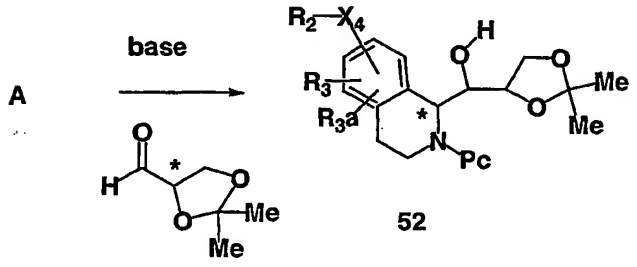
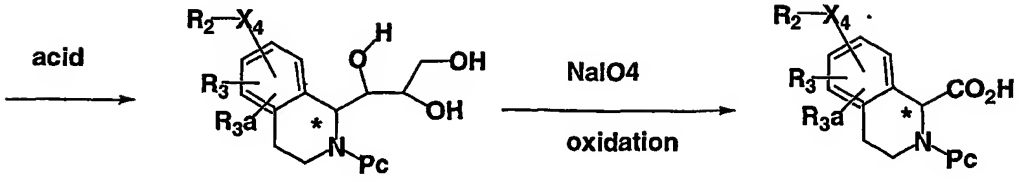
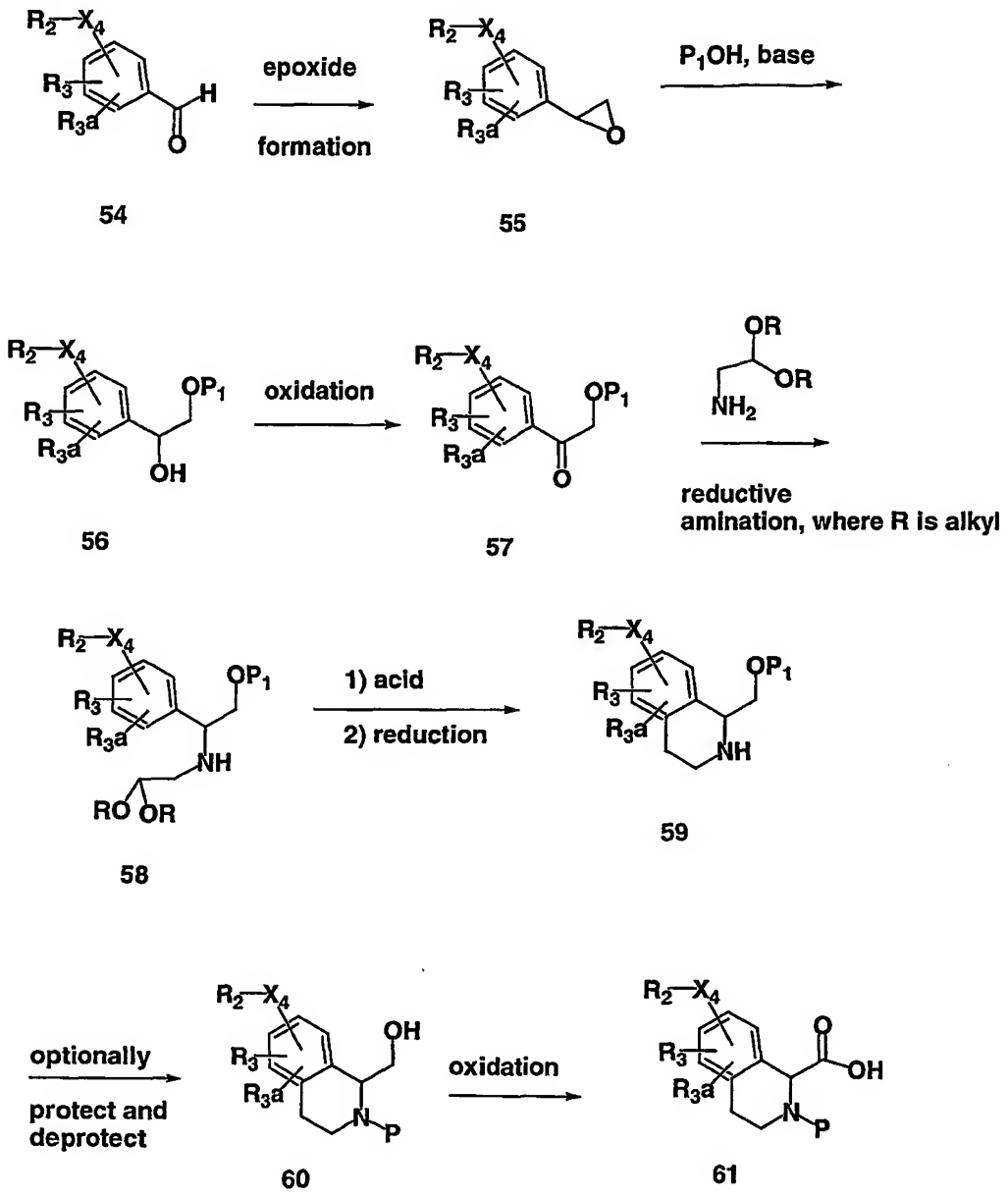


51: D, L, or DL

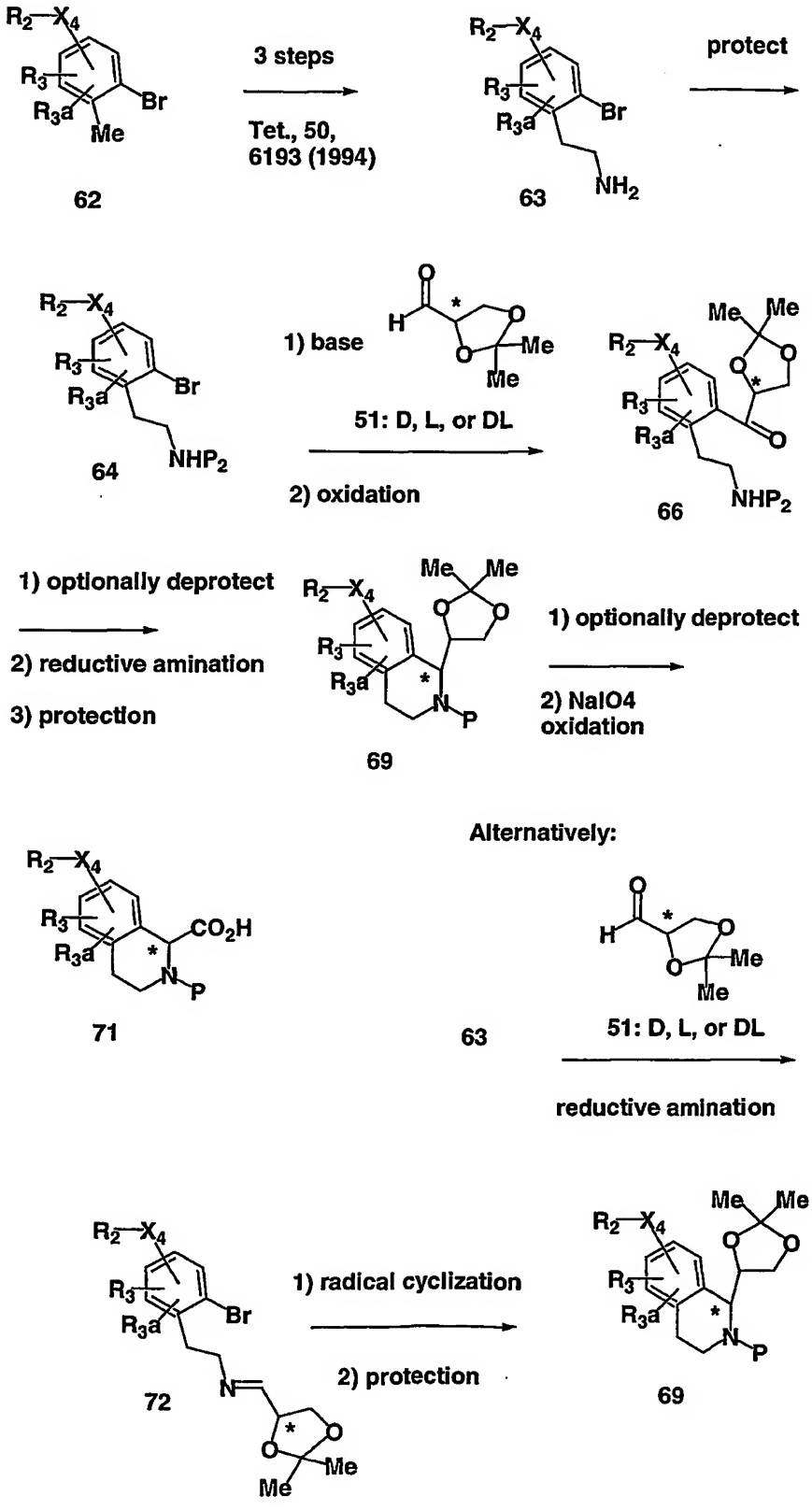


53 49

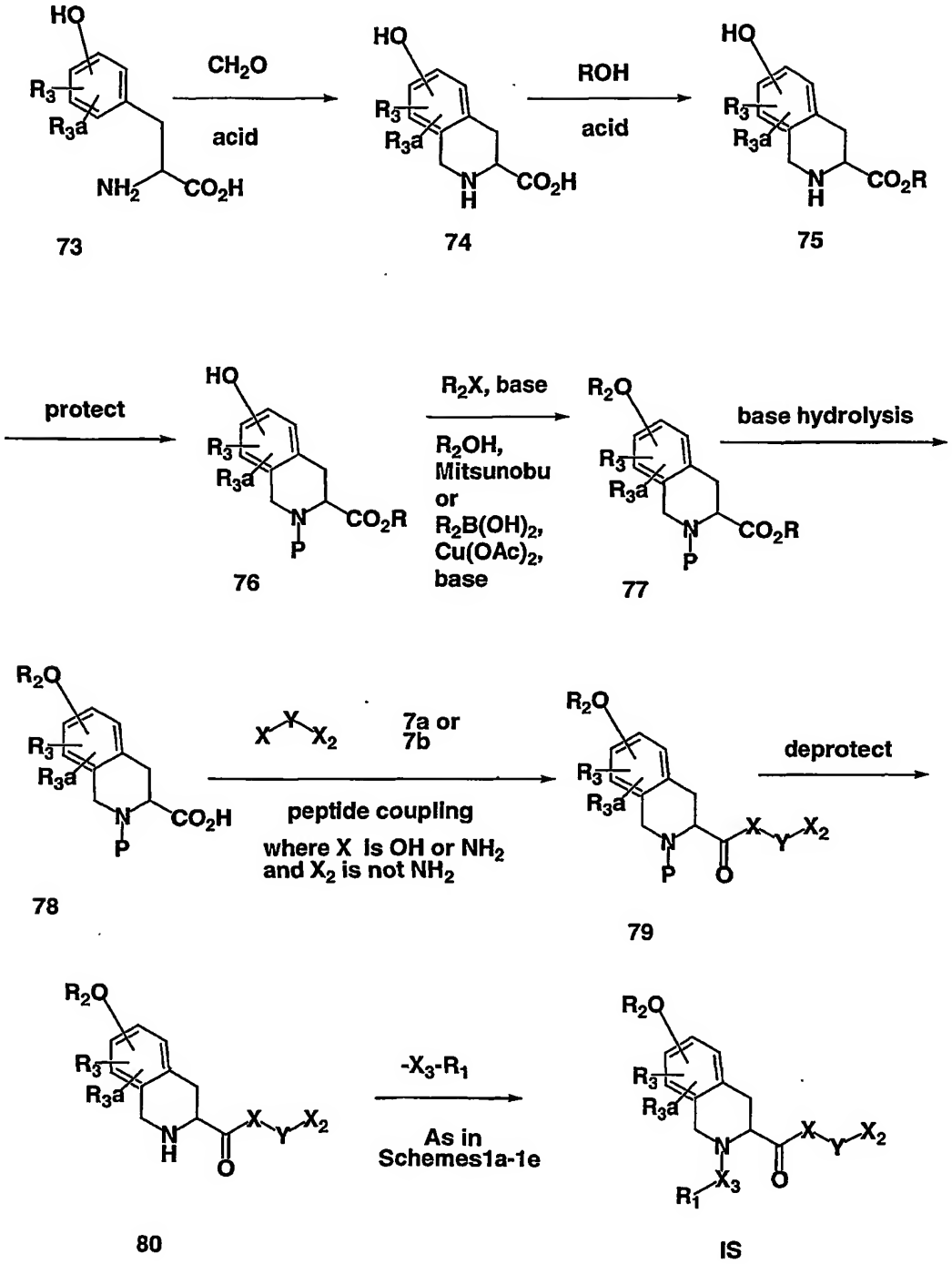
General Scheme 9: Alternate Routes to Core



General Scheme 10: Alternate Routes to Core



Scheme 11: Alternate Core



The growth hormone releasing compounds of formula I can be administered to animals, including man, to release growth hormone in vivo. For example, the compounds can be administered to commercially important animals such as swine, cattle, sheep and the like to accelerate and increase their rate and extent of growth, and to increase milk production in such animals.

The present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of formula I in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise a growth promoting agent in addition to at least one of the compounds of formula I or another composition which exhibits a different activity, e.g., an antibiotic or other pharmaceutically active material.

Growth promoting agents include, but are not limited to, TRH, diethylstilbesterol, theophylline, enkephalins, E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

A still further use of the disclosed compounds of formula I of the invention is in combination with other growth hormone secretagogues such as GHRP-6, GHRP-1 as described in U.S. Patent No. 4,411,890; and publications WO 89/07110 and WO 89/07111 and B-HT920 or growth hormone releasing factor and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2. A still further use of the disclosed compounds of formula I of the invention is in combination with parathyroid hormone or bisphosphonates, such as MK-217 (alendronate), in the treatment of osteoporosis.

A still further use of the disclosed compounds of formula I is in combination with estrogen, testosterone,

a selective estrogen receptor modulator, such as tamoxifen or raloxifene, or a selective androgen receptor modulator, such as disclosed in Edwards, J. P. et al., *Bio. Med. Chem. Let.*, 9, 1003-1008 (1999) and Hamann, L. G. et al., *J. Med. Chem.*, 42, 210-212 (1999), for the treatment of aspects of Metabolic Syndrome, maintenance of muscle strength and function in elderly humans, reversal or prevention of frailty in elderly humans, stimulation and increase in muscle mass and muscle strength, attenuation of protein catabolic response after a major operation or trauma; reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; improvement in muscle mobility, and maintenance of skin thickness.

A further use of the compounds of this invention is in combination with progestin receptor agonists ("PRA").

As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous. Thus, the administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself.

To those skilled in the art, it is well known that the current and potential uses of growth hormone are varied and multitudinous. Thus, compounds of formula I can be administered for purposes stimulating release of endogenous growth hormone and would thus have similar effects or uses as growth hormone itself. Compounds of formula I are useful for stimulation of growth hormone release (e.g., in the elderly); maintenance of muscle strength and function (e.g., in the elderly); reversal or prevention of frailty or age-related functional decline ("ARFD") in the elderly; prevention of catabolic side effects of glucocorticoids; prevention and treatment of osteoporosis; treatment of chronic fatigue syndrome (CFS); treatment of acute fatigue syndrome and muscle loss following election surgery; stimulation of the

immune system, including improvement of immune response to vaccination; acceleration of wound healing; accelerating bone fracture repair (such as accelerating the recovery of hip fracture patients); accelerating healing of complicated fractures, e.g. disctraction osteogenesis; acceleration of tooth repair or growth; maintenance of sensory function (e.g., hearing, sight, olefaction and taste); treatment of wasting secondary to fractures; treatment of growth retardation; treatment of growth retardation resulting from renal failure or insufficiency; treatment of cardiomyopathy; treatment of wasting in connection with chronic liver disease; treatment of thrombocytopenia; treatment of growth retardation in connection with Crohn's disease; treatment of short bowel syndrome; treatment of irritable bowel syndrome; treatment of inflammatory bowel disease; treatment of Crohn's disease and ulcerative colits; treatment of wasting in connection with chronic obstructive pulmonary disease (COPD); treatment of complications associated with transplantation; treatment of physiological short stature including growth hormone deficient children and short stature associated with chronic illness; treatment of obesity and growth retardation associated with obesity; treatment of anorexia (e.g., associated with cachexia or aging); treatment of growth retardation associated with the Prader-Willi syndrome and Turner's syndrome; increasing the growth rate of a patient having partial growth hormone insensitive syndrome; accelerating the recovery and reducing hospitalization of burn patients; treatment of intrauterine growth retardation, skeletal dysplasia, hypercortisolism and Cushing's syndrome; induction of pulsatile growth hormone release; replacement of growth hormone in stressed patients; treatment of osteochondrodysplasias; treatment of Noonan's syndrome; treatment of schizophrenia; treatment of depression; improvement of cognitive function (e.g., treatment of

dementia; treatment of Alzheimer's disease; treatment of delayed wound healing and psychosocial deprivation; treatment of catabolism in connection with pulmonary dysfunction and ventilator dependency; treatment of cardiac dysfunction (e.g. associated with valvular disease, myocarial infarction, cardiac hypertrophy or congestive heart failure); lowering blood pressure; protection against ventricular dysfunction or prevention of reperfusion events; treatment of adults in chronic dialysis; reversal or slowing of the catabolic state of aging; attenuation or reversal of protein catabolic responses following trauma (e.g., reversal of the catabolic state associated with surgery, congestive heart failure, cardiac myopathy, burns, cancer, COPD etc.); reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; treatment of hyperinsulinemia including nesidioblastosis; adjuvant treatment for ovulation induction; stimulation of thymic development and prevention of the age-related decline of thymic function; treatment of immunosuppressed patients; treatment of sarcopenia; treatment of wasting in connection with AIDS; treatment of wasting in connection with multiple sclerosis or other neurodegenerative disorders; improvement in muscle strength, mobility, maintenance of skin thickness; hair/nail growth; treatment of metabolic homeostasis and renal homeostasis (e.g., in the frail elderly); stimulation of osteoblasts, bone remodelling and cartilage growth; regulation of food intake; stimulation of the immune system in companion animals and treatment of disorders of aging in companion animals; promoting growth in livestock; stimulation of wool growth in sheep; increasing milk production in livestock; treatment of insulin resistance including NIDDM, in mammals (e.g. humans); treatment of insulin resistance in the heart; improvement of sleep quality and correction of the relative hyposomatotropism of senescence due to high increase in REM sleep and a

decrease in REM latency; treatment of hypothermia; treatment of frailty such as that associated with aging; treatment of congestive heart failure; treatment of hip fractures; treatment of immune deficiency in individuals with a depressed T4/T8 cell ratio; treatment of lipodystrophy (e.g., in patients taking HIV or AIDS therapies such as protease inhibitors); treatment of muscular atrophy (e.g., due to physical inactivity, bed rest or reduced weight-bearing conditions); treatment of musculoskeletal impairment (e.g., in elderly); enhancing the activity of protein kinase B (PKB); improvement of the overall pulmonary function; treatment of sleep disorders; and the treatment of the catabolic state of prolonged critical illness. The term treatment is also intended to include prophylactic treatment.

In addition, the conditions, diseases, and maladies collectively referenced to as "Syndrome X" or Metabolic Syndrome as detailed in Johannsson *J. Clin. Endocrinol. Metab.*, 82, 727-34 (1997), may be treated employing the compounds of the invention.

The compounds of the present invention are agents that are growth hormone secretagogues and can be administered to various mammalian species, such as monkeys, dogs, cats, rats, humans, etc., in need of treatment. These agents can be administered systemically, such as orally or parenterally.

The compounds of the invention can be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable formulation. The above dosage forms will also include the necessary physiologically acceptable carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral, intranasal or aerosol forms are quite satisfactory as well.

The dose administered must be carefully adjusted according to the age, weight, and condition of the patient, as well as the route of administration, dosage form and regimen, and the desired result. In general, the dosage forms described above may be administered in amounts from about 0.0001 to about 100 mg/kg or body weight or in an amount within the range from about 1 to about 1000 mg per day, preferably, from about 5 to about 500 mg per day in single or divided doses of one to four times daily.

The compounds of the present invention may be employed alone or in combination with each other and/or other growth hormone secretagogues or other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: Anti-diabetic agents; anti-osteoporosous agents; anti-obesity agents; anti-inflammatory agents; anti-anxiety agents; anti-depressants; anti-hypertensive agents; anti-platelet agents; anti-thrombotic and thrombolytic agents; cardiac glycosides; cholesterol/lipid lowering agents; mineralocorticoid receptor antagonists; phospodiesterase inhibitors; protein tyrosine kinase inhibitors; thyroid mimetics (including thyroid receptor antagonists); anabolic agents; HIV or AIDS therapies; therapies useful in the treatment of Alzheimer's disease and other cognitive disorders; therapies useful in the treatment of sleeping disorders; anti-proliferative agents; anti-tumor agents; and/or anti-ulcer and gastroesopheageal reflux disease agents.

Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include biguanides (e.g. metformin), glucosidase inhibitors (e.g. acarbose), insulins (including insulin secretagogues or insulin sensitizers), meglitinides (e.g. repaglinide), sulfonylureas (e.g., glimepiride, glyburide and glipizide), biguanide/glyburide combinations (e.g.,

glucovance), thiozolidinediones (e.g. troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, inhibitors of fatty acid binding protein (aP2) such as those disclosed in U.S. Serial No. 09/519,079 filed March 6, 2000 (attorney docket LA27), glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DP4) inhibitors.

Examples of suitable anti-osteoporosous agents for use in combination with the compounds of the present invention include alendronate, risedronate, raloxifene, calcitonin, non-steroidal progestin receptor agonists, RANK ligand agonists, calcium sensing receptor antagonists, TRAP inhibitors, selective estrogen receptor modulators (SERM), estrogen and AP-1 inhibitors;

Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include aP2 inhibitors such as those disclosed in U.S. Serial No. 09/519,079 filed March 6, 2000 (attorney docket LA27), PPAR gamma antagonists, PPAR delta agonists, and orlistat.

Examples of suitable antinflammatory agents for use in combination with the compounds of the present invention include prednisone, dexamethasone, Enbrel, cyclooxygenase inhibitors (i.e., COX-1 and/or COX-2 inhibitors such as NSAIDs, aspirin, indomethacin, ibuprofen, piroxicam, Naproxen, Celebrex, Vioxx), CTLA4-Ig agonists/antagonists, CD40 ligand antagonists, integrin antagonists, alpha4 beta7 integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, ICAM-1, tumor necrosis factor (TNF) antagonists (e.g., infliximab, OR1384), prostaglandin synthesis inhibitors, budesonide, clofazimine, CNI-1493, CD4 antagonists (e.g., priliximab), p38 mitogen-activated protein kinase inhibitors, protein tyrosine kinase (PTK) inhibitors, IKK inhibitors, and therapies for the treatment of irritable

bowel syndrome (e.g., zelmac and Maxi-K openers such as those disclosed in U.S. Patent No. 6,184,231 B1).

Example of suitable anti-anxiety agents for use in combination with the compounds of the present invention include diazepam, lorazepam, buspirone, oxazepam, and hydroxyzine pamoate.

Examples of suitable anti-depressants for use in combination with the compounds of the present invention include citalopram, fluoxetine, nefazodone, sertraline, and paroxetine.

Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include beta adrenergic blockers, calcium channel blockers (L-type and T-type; e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diruetics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

Examples of suitable anti-platelet agents for use in combination with the compounds of the present invention include GPIIb/IIIa blockers (e.g., abciximab, eptifibatide, tirofiban), P2Y12 antagonists (e.g., clopidogrel, ticlopidine, CS-747), thromboxane receptor

antagonists (e.g., ifetroban), aspirin, and PDE-III inhibitors (e.g., dipyridamole) with or without aspirin.

Examples of suitable cardiac glycosides for use in combination with the compounds of the present invention include digitalis and ouabain.

Examples of suitable cholesterol/lipid lowering agents for use in combination with the compounds of the present invention include HMG-CoA reductase inhibitors (e.g., pravastatin lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, or nisvastatin or nisbastatin) and ZD-4522 (a.k.a. rosuvastatin, or atavastatin or visastatin)), squalene synthetase inhibitors, fibrates, bile acid sequestrants, ACAT inhibitors, MTP inhibitors, lipooxygenase inhibitors, choesterol absorption inhibitors, and cholesterol ester transfer protein inhibitors (e.g., CP-529414).

Examples of suitable mineralocorticoid receptor antagonists for use in combination with the compounds of the present invention include spironolactone and eplerinone.

Examples of suitable phospodiesterase inhibitiors for use in combination with the compounds of the present invention include PDEIII inhibitors such as cilostazol, and PDE V inhibitors such as sildenafil.

Examples of suitable thyroid mimetics for use in combination with the compounds of the present invention include thyrotropin, polythyroid, KB-130015, and dronedarone.

Examples of suitable anabolic agents for use in combination with the compounds of the present invention include testosterone and SARMs.

Examples of suitable HIV or AIDS therapies for use in combination with the compounds of the present invention include indinavir sulfate, saquinavir, saquinavir mesylate, amprenavir, ritonavir, lopinavir, ritonavir/lopinavir combinations, lamivudine, zidovudine,

lamivudine/zidovudine combinations, zalcitabine, didanosine, stavudine, and megestrol acetate.

Examples of suitable therapies for treatment of Alzheimer's disease and cognitive disorders for use in combination with the compounds of the present invention include donepezil, tacrine, revastigmine, 5HT6, gamma secretase inhibitors, beta secretase inhibitors, SK channel blockers, Maxi-K blockers, and KCNQs blockers.

Examples of suitable therapies for treatment of sleeping disorders for use in combination with the compounds of the present invention include melatonin analogs, melatonin receptor antagonists, ML1B agonists, and GABA/NMDA receptor antagonists.

Examples of suitable anti-proliferative agents for use in combination with the compounds of the present invention include cyclosporin A, taxol, FK 506, and adriamycin.

Examples of suitable anti-tumor agents for use in combination with the compounds of the present invention include taxol, adriamycin, epothilones, cisplatin and carboplatin.

Compounds of the present invention may further be used in combination with nutritional supplements such as those described in U.S. 5,179,080, especially in combination with whey protein or casin, amino acids (such as leucine, branched amino acids and hydroxymethylbutyrate), triglycerides, vitamins (e.g., A, B6, B12, folate, C, D and E), minerals (e.g., selenium, magnesium, zinc, chromium, calcium and potassium), carnitine, lipoic acid, creatine, and coenzyme Q-10.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

The following Examples represent preferred embodiments of the invention. All temperatures are in °C unless indicated otherwise.

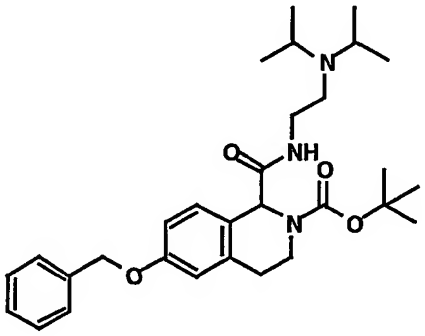
General Experimental:

HPLCa: Shimadzu, 0-100% B [MeOH:H_2O:0.2% H_3PO_4], 4 min. gradient, 1 min. hold, 220nM, YMC S5 ODS 4.6 x 50 mm.

HPLCa1: Shimadzu, 0-100% B [MeOH: H_2O:0.2% H_3PO_4], 2 min. gradient, 1 min. hold, 220nM, YMC S5 ODS4.6 x 33 mm.

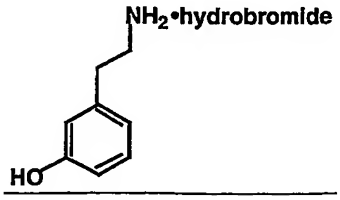
HPLCb: Shimadzu, 0-100% B [MeOH:H_2O:0.1% TFA], 4 min. gradient, 1 min. hold, 220nM, YMC S5 ODS 4.6 x 50 mm.

Example 1



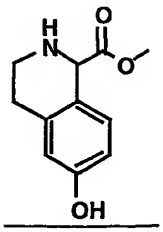
1-[[[2-[Bis(1-methylethyl)amino]ethyl]amino]carbonyl]-3,4-dihydro-6-(phenylmethoxy)-2(1H)-isoquinoline-carboxylic acid, 1,1-dimethylethyl ester.

A.



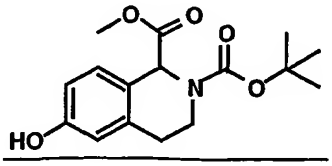
Hydrobromic acid (48%, 500 mL) was added to 3-methoxyphenethylamine (150 g, 0.992 mmol). The formed white solid dissolved upon warming. The reaction mixture was heated at reflux for 3 days. Water was removed by coevaporation with toluene to give the title compound (298 g, >100%) as a white solid%): LC/MS (electrospray, + ions) m/z 138(M+H).

B.



A mixture of Part A compound (266 g, 1.22 mol), glyoxylic acid monohydrate (130 g, 1.41 mol) and 5% hydrochloric acid solution (2 L) was warmed at 80°C under nitrogen for 8 h. Water was removed by azeotroping with toluene. The residue was dissolved in methanol (1500 mL), and then chlorotrimethylsilane (200 mL, 1.58 mol) was added. The suspension became clear after warming to 49°C. Stirring was continued at 49°C for 12 h. The reaction mixture was concentrated, and the residue was treated with saturated aqueous sodium bicarbonate solution to make it basic. The aqueous solution (saturated with sodium chloride) was extracted with ethyl acetate (6 x 300 mL) until no product was visible in the aqueous layer by TLC. Solvent was removed *in vacuo*. Ethanol was added to the residue, and the yellow solid that formed was collected by filtration to give the title compound (87 g, 35%): LC/MS (electrospray, + ions) m/z 208(M+H).

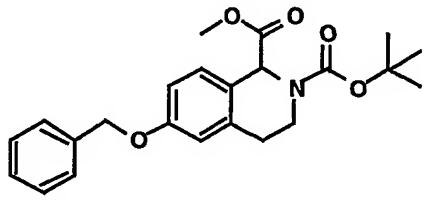
C.



A solution of di-*tert*-butyl dicarbonate (89 g, 0.40 mol) in tetrahydrofuran (500 mL) was slowly added to a suspension of Part B compound (76 g, 0.37 mol) in tetrahydrofuran (800 mL) and triethylamine (5 mL, 0.036

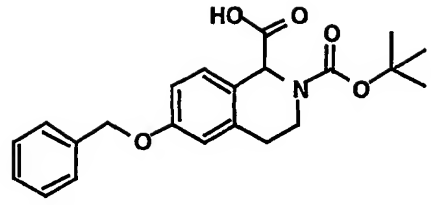
mol). The reaction was stirred at ambient temperature for 2 h until bubbling stopped. The reaction solution was passed through a pad of silica gel, rinsing with tetrahydrofuran. The solvent was removed, and the residue was dissolved in ethyl acetate (400 mL). The ethyl acetate solution was washed with water (500 mL), 10% aqueous citric acid solution (200 mL) and brine. The organic layer was dried over sodium sulfate, and the mixture was filtered. The filtrate was concentrated to give the title compound (128 g, 100%) as a light brown oil: LC/MS (electrospray, + ions) m/z 308(M+H).

D.



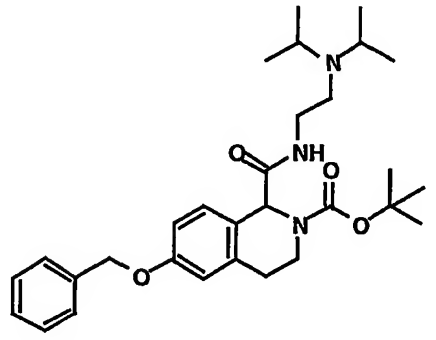
A mixture of Part C compound (48.0 g, 0.156 mol), benzyl bromide (25 mL, 0.209 mol) and potassium carbonate (74 g, 0.536 mol) in dimethylformamide (500 mL) was stirred overnight. The reaction mixture was filtered, rinsing with ethyl acetate, and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate, and the organic solution was washed with water followed by 10% aqueous citric acid solution (2x) and brine and then dried over sodium sulfate. The mixture was filtered and the filtrate concentrated. Purification by silica gel column chromatography, eluting with 10% ethyl acetate in heptane (6 L) followed by 20% ethyl acetate in heptane (4 L), gave the title compound (58.0 g, 93%) as a white foam.

E.



Part D compound (21.51 g, 54.12 mmol) was dissolved in methanol (50 mL) and tetrahydrofuran (50 mL), and then water (50 mL) was added. To the resultant milky mixture was added sodium hydroxide (6.49 g, 162.3 mmol). Within 10 min, the reaction temperature rose from 23°C to 40°C, and the reaction became clear. After stirring for 2.5 h, the reaction mixture was transferred to a separatory funnel and water (50 mL) was added. The product was extracted with ethyl acetate (2 x 250 mL). The rich organic layer was washed with 1 N hydrochloric acid solution (250 mL) followed by brine (100 mL) and dried over sodium sulfate. The mixture was filtered, and the filtrate was concentrated and dried *in vacuo* to give the title compound (17.3 g, 83%) as a white foam: LC/MS (electrospray, + ions) m/z 382(M+H).

F.



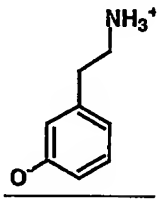
A solution of Part E compound (500 mg, 1.3 mmol) in dimethylformamide (3 mL) was treated with diisopropylethylenediamine (248 µL, 1.37 mmol) followed

by 1-hydroxy-7-azabenzotriazole (213 mg, 1.56 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (300 mg, 1.56 mmol). The mixture was stirred overnight at ambient temperature. Evaporation of the solvent gave a residue, which was dissolved in dichloromethane. The dichloromethane solution was washed with water (3 x 30 mL) and dried over magnesium sulfate. The mixture was filtered, and the filtrate was concentrated. Silica gel flash column chromatography purification gave the title product (523 mg, 79%) as a white solid: LC/MS (electrospray, + ions) m/z 510(M+H).

Example 1A

An alternative procedure for the preparation of Example 1 Part B compound follows:

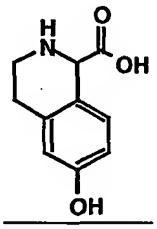
A.



A solution of 48% hydrobromic acid (100 mL) was added slowly and cautiously to a flask at 4°C containing *m*-methoxyphenethylamine (50 g, 0.331 mol). The amine salt formed as a white solid. The reaction mixture was heated at 140°C under gentle reflux for 18 h. After cooling, the solvent was evaporated to give a white residue, which was further dried under high vacuum. The solid was then dissolved in water, and dichloromethane was added to extract the non-polar impurities. The aqueous layer was made alkaline by the addition of powdered sodium carbonate. Water was evaporated to give a white solid, which was dried *in vacuo*. The extraction of the product was done by the addition of ethyl acetate,

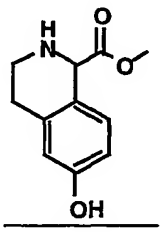
with heating at reflux. Molecular sieves (4 Å) were added to absorb the residual water. The mixture was decanted. The ethyl acetate extraction was repeated until only trace amounts of product were present in the extract. The ethyl acetate extracts were combined. Ethyl acetate was evaporated to give the title product (29 g, 64%) as a white solid.

B.



To a 4°C solution of Part A compound (3.08 g, 22.5 mmol) in denatured ethanol (70 mL) was added a solution of glyoxylic acid monohydrate (2.0 g, 22 mmol) in ethanol (10 mL) dropwise. Shortly after the addition of glyoxylic acid, a white precipitate formed. The cooling bath was removed, and the reaction mixture was stirred for 2 h at ambient temperature. Filtration gave the title product (3.1 g, 73%) as a white solid: LC/MS (electrospray, + ions) m/z 194(M+H).

C.



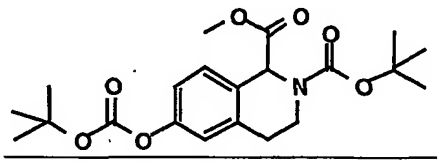
A solution of hydrogen chloride in methanol (150 mL), prepared by the addition of acetyl chloride (13 mL) to methanol (500 mL), was added to Part B compound (6.0

g, 31.1 mmol). The mixture was heated at reflux for 48 h. The solvent was evaporated to give a white residue, to which ethyl acetate and saturated aqueous sodium carbonate were added. The two layers were separated, and extraction of the aqueous layer with ethyl acetate was repeated several times. The ethyl acetate layers were combined and dried over magnesium sulfate. The mixture was filtered, and the filtrate was concentrated to give the title product (3.93 g, 61%) as a yellow solid: LC/MS (electrospray, + ions) m/z 208(M+H).

Example 1B

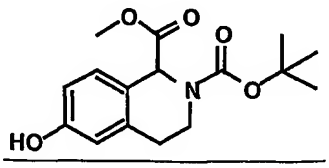
An alternative procedure for the preparation of Example 1 Part C compound follows:

A.



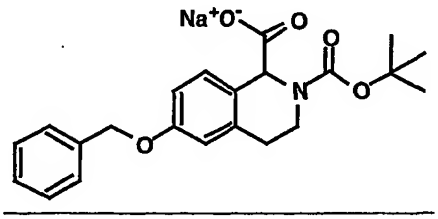
To a mixture of Example 1 Part B compound (3.0 g, 14.5 mmol) and di-*tert*-butyl dicarbonate (8.21 g, 37.6 mmol) was added tetrahydrofuran (75 mL). This mixture was stirred to give a slurry. Triethylamine (5.3 mL, 38.0 mmol) was added, and the reaction mixture was stirred at ambient temperature for 18 h. The title compound was used in the next step without work-up.

B.



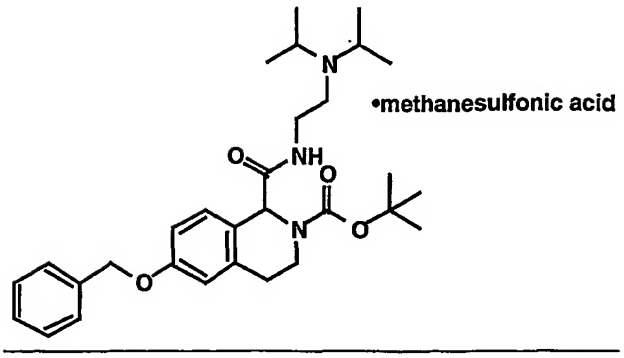
To the reaction mixture containing Part A compound was added methanol (30 mL) and then 25 wt% sodium methoxide in methanol (15 mL). The resultant viscous reaction mixture was stirred at ambient temperature for 2 h. A solution of 10% acetic acid in water (50 mL) was added. The reaction temperature rose from 22°C to 34°C, and gas evolution was observed. Tetrahydrofuran and methanol were removed by rotovaporation. The product was extracted with dichloromethane (2 x 50 mL). The organic layer was washed with water (50 mL) and brine (25 mL) and dried over sodium sulfate. The mixture was filtered, and the filtrate was concentrated to give the title product (4.6 g) as a white foam: LC/MS (electrospray, + ions) m/z 308(M+H).

Example 2



To a solution of Part D compound from Example 1 (0.60 g, 1.51 mmol) in tetrahydrofuran (6 mL) was added 1 N sodium hydroxide solution (6 mL, 6 mmol). After stirring for 45 h, the reaction mixture was transferred to a separatory funnel, and the product was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined and washed with 1 N sodium hydroxide solution (5 mL) and brine (5 mL) and then dried over anhydrous sodium sulfate. The mixture was filtered, and the filtrate was concentrated and dried *in vacuo* to give the title compound (0.41 g, 67%) as a white solid.

Example 3

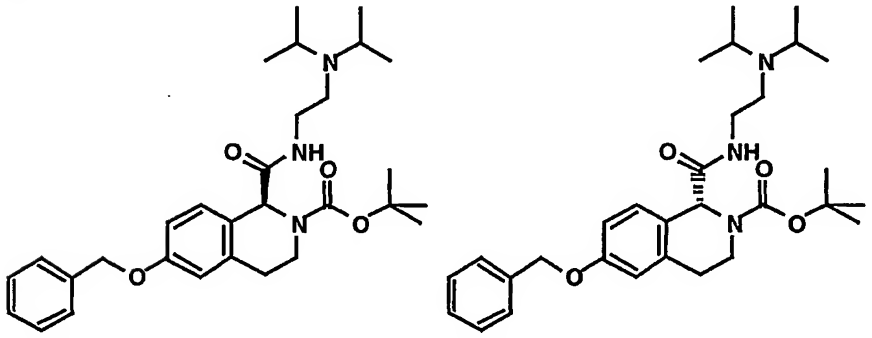


To a solution of Part F compound from Example 1 (107 mg, 0.210 mmol) in dichloromethane (10 mL) was added methanesulfonic acid (16 µL, 0.247 mmol). The solvent was evaporated, and the residue was dissolved in acetone. Hexanes was then added. Concentration gave the title product (110 mg, 86%) as a white solid: LC/MS (electrospray, + ions) m/z 510 (M+H).

Example 4

Isomer A and Isomer B

A.



Example 1, title compound (2 batches of 500 mg) was resolved on Chiralpak OD column (50 x 500 mm), eluting with 20% isopropanol in hexanes to give the title compounds, Isomer A (0.350 g, 35%) and Isomer B (0.356 g, 36%).

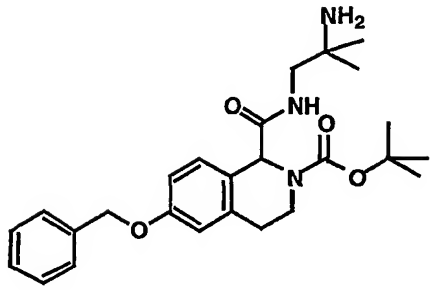
Isomer A

[α]D = -22.7° (c = 0.1; methanol)

Isomer B

[α]D = +28.4° (c = 0.1; methanol)

Example 5



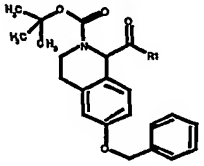
A solution of Part E compound from Example 1 (100 mg, 0.26 mmol) in dimethylformamide was treated with 1,2-diamino-2-methylpropane (27 µL, 0.26 mmol) followed by 1-hydroxy-7-azabenzotriazole (42 mg, 0.31 mmol) and 1,3-diisopropylcarbodiimide (50 µL, 0.32 mmol), and the reaction mixture was stirred overnight at ambient temperature. The crude reaction mixture was loaded onto a SCX column that had been washed with methanol. The column was washed with methanol (3 x 10 mL) and then the product was eluted from the column with 2.0 M ammonia in methanol (6 mL). Evaporation of the solvent gave the title product (109 mg, 92%) as a white solid: LC/MS (electrospray, + ions) m/z 454 (M+H).

Examples 6 to 26

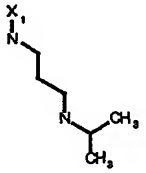
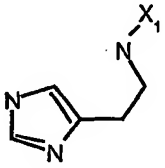
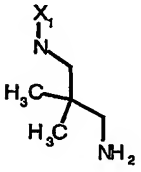
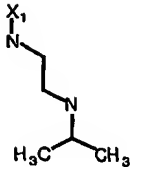
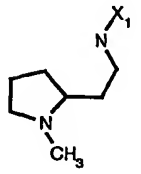
In a manner analogous to that of Example 5, Examples 6-26 listed in the table below were prepared from Part E compound of Example 1 and the respective amines. Examples 6 to 26 compounds were purified by preparative HPLC, eluting with a gradient system of methanol and water with 0.2% trifluoroacetic acid and neutralized with sodium bicarbonate. Example 19-26

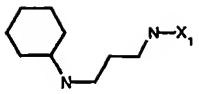
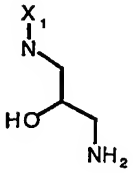
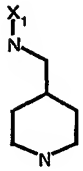
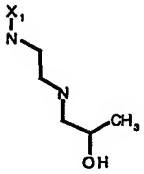
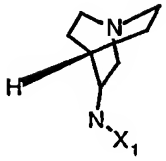
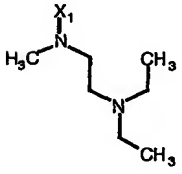
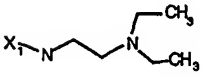
compounds were prepared as methanesulfonic acids in a manner analogous to that of Example 3, except that exactly one equivalent of methanesulfonic acid was used.

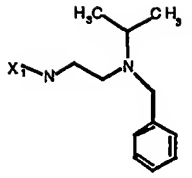
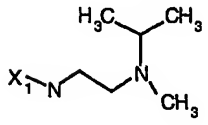
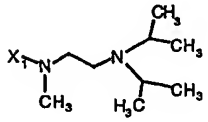
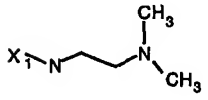
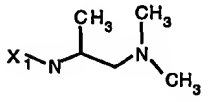
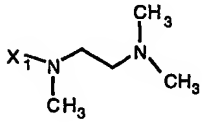
In the tables of compounds which follow, the X_1 designation refers to the point of attachment of the particular R1 moiety shown to the remainder of the molecule.



= X_1-R1

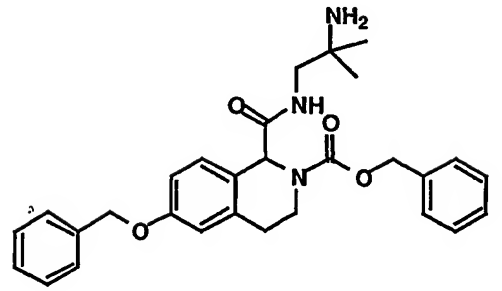
Example No.	X_1-R1	LC/MS $(M + H)^+$
6		482
7		477
8		491
9		468
10		468
11		494

12		522
13		456
14		480
15		484
16		470
17		466
18		492
19		496
20		482

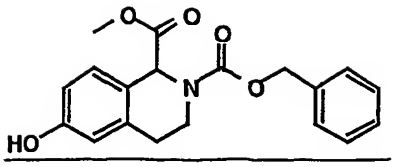
21		558
22		482
23		524
24		454
25		468
26		468

Example 27

5

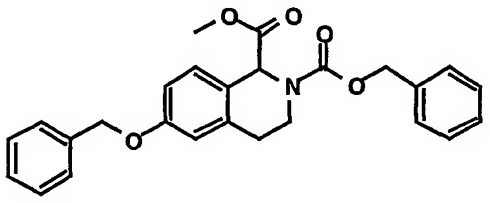


A.



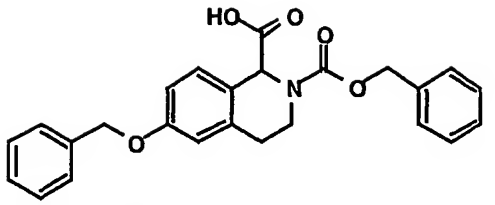
To a suspension of Part B compound from Example 1 (5.0 g, 24 mmol) in dichloromethane (100 mL) was added triethylamine (4.0 mL, 29 mmol). The mixture was cooled to 4°C and benzylchloroformate (4.1 mL, 29 mmol) was added dropwise. The reaction mixture became clear and was stirred for 15 min. Additional dichloromethane was added and was washed with water followed by ~5% citric acid solution. The organic layer was dried over magnesium sulfate, and the mixture was filtered. The filtrate was concentrated to give the title compound (8.0 g, 97%) as a yellow solid.

B.



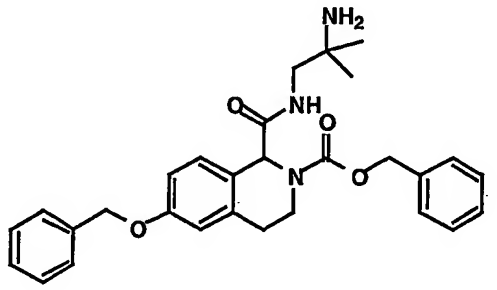
A heterogeneous mixture of Part A compound (8.0 g, 23.5 mmol), benzyl bromide (4.33 g, 23.5 mmol) and potassium carbonate (13 g, 94.1 mmol) in dimethylformamide (20 mL) was stirred at ambient temperature overnight. The reaction mixture was concentrated, and the residue was dissolved in ethyl acetate (300 mL). The organic layer was washed with water (3 x 200 mL) and dried over magnesium sulfate. The mixture was filtered, and the filtrate was concentrated. Flash column chromatography (1:1 ethyl acetate/hexanes) gave the title product (9.2 g, 91%) as a yellow syrup.

C.



A solution of the methyl ester from Part B compound (3.6 g, 8.38 mmol) in methanol (3 mL) and tetrahydrofuran (3 mL) was treated with 10 M aqueous sodium hydroxide (2 mL, 20 mmol) and stirred at ambient temperature for 2 h. The reaction solution was acidified with 2 N hydrochloric acid solution to pH ~1-2. The product was extracted with ethyl acetate. The organic layer was washed with brine (2x) and dried over magnesium sulfate. The mixture was filtered, and the filtrate was concentrated to give the title product (3.0 g, 86%) as a yellow solid: LC/MS (electrospray, + ions) m/z 418(M+H).

D.

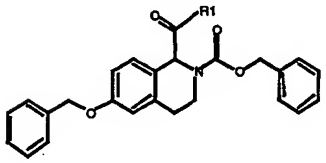


A solution of Part C compound (100 mg, 0.24 mmol) in dimethylformamide (3 mL) was treated with 1,2-diamino-2-methylpropane (30 µL, 0.29 mmol) followed by 1-hydroxy-7-azabenzotriazole (40 mg, 0.29 mmol) and 1,3-diisopropylcarbodiimide (45 µL, 0.29 mmol). The reaction mixture was stirred at ambient temperature overnight. The solvent was removed, and the residue was dissolved in methanol. This solution was applied to a CUBC x 12M6 column, which was prewashed with methanol (10 mL). The

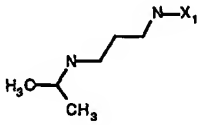
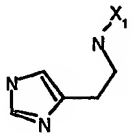
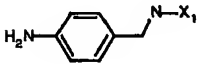
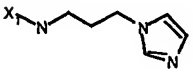
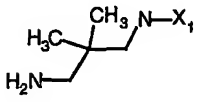
column was washed with methanol (3 x 10 mL), and then the product was eluted with 2 M ammonium in methanol (10 mL). Evaporation of the solvent gave the title compound (110 mg, 94%) as a white solid: LC/MS (electrospray, + ions) m/z 488 (M+H).

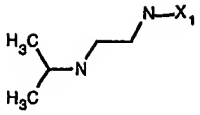
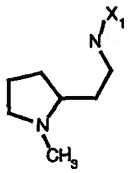
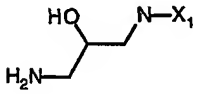
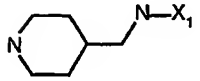
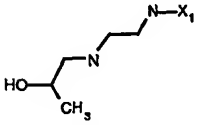
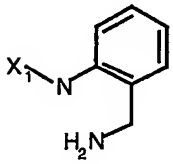
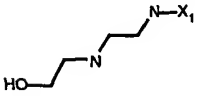
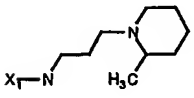
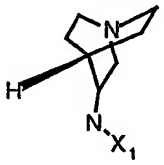
Examples 28 to 45

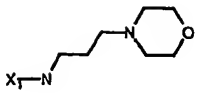
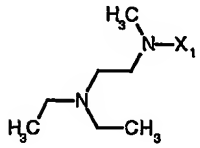
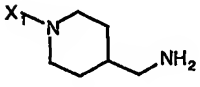
In a manner analogous to that of Example 27, Examples 28-45 listed in the table below were prepared from Part C compound of Example 27 and the respective amines. Examples 38 and 45 compounds were purified by preparative HPLC, eluting with a gradient system of methanol and water with 0.2% trifluoroacetic acid. These compounds were isolated as trifluoroacetic acid salts.



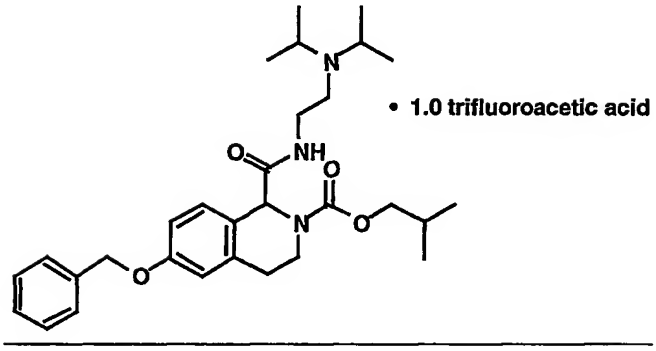
= X_1-R1

Example No.	X_1-R1	LC/MS $(M + H)^+$
28		516
29		511
30		522
31		525
32		502

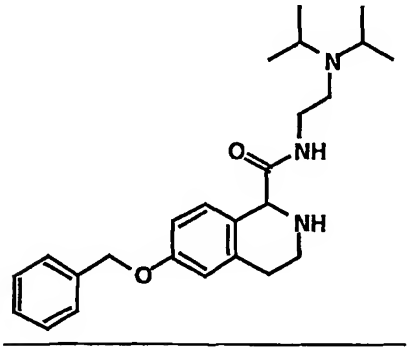
33		502
34		528
35		490
36		514
37		518
38		522
39		504
40		500
41		556
42		526

43		544
44		530
45		514

Example 46



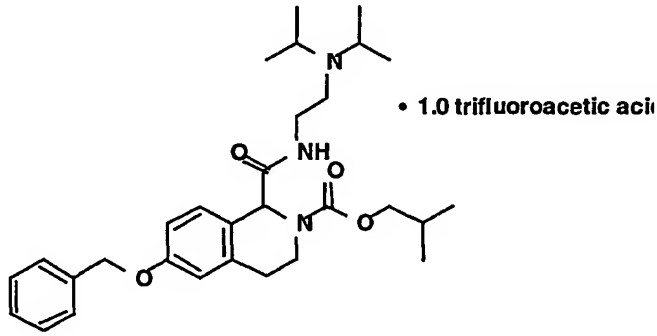
A.



To a flask containing Example 1, title compound, (1.57 g, 3.1 mol) was slowly added 4 N hydrogen chloride in dioxane (10 mL, 40 mol) with a syringe at ambient temperature. It was stirred for 1 h and then

concentrated. The residue was dissolved in ethyl acetate and then the pH was adjusted to ~pH 8 with the addition of 1 N sodium hydroxide solution. The ethyl acetate layer was separated and dried over sodium sulfate. The mixture was filtered and the filtrate concentrated to give the title compound (1.13 g, 89%) as a yellow oil: LC/MS (electrospray, + ions) m/z 410(M+H).

B.

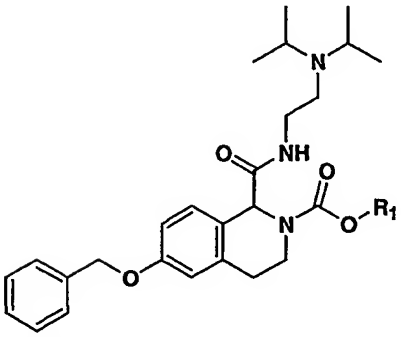


To a 4°C solution of Part A compound (60.0 mg, 0.147 mmol) and triethylamine (30 µL, 0.215 mmol) in tetrahydrofuran (10 mL) was added isobutyl chloroformate (28.5 µL, 0.220 mmol). The mixture was stirred at 0°C to 10°C for 1 h. The mixture was concentrated, and the concentrate was purified by preparative HPLC, eluting with a gradient system of 30-100% B (where A = 90% water, 10% methanol, 0.2% trifluoroacetic acid and B = 90% methanol, 10% water, 0.2% trifluoroacetic acid), to give the title compound (81 mg, 89%) as a yellow oil:HPLCa rt = 3.99 min; LC/MS (electrospray, + ions) m/z 510(M+H).

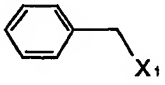
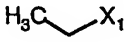
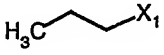
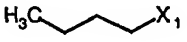
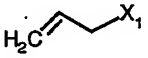
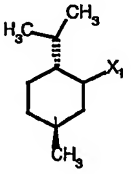
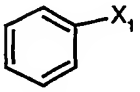
Example 47 to 54

In a manner analogous to that of Example 46, Examples 47-54 compounds listed in the table below were

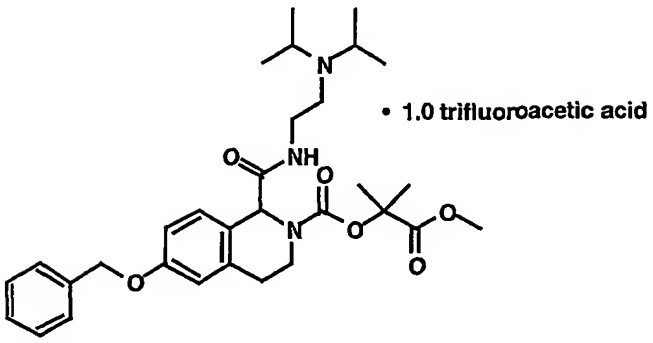
prepared from Part A compound from Example 46 and the respective chloroformate.



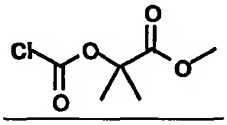
= X_1-R1

Example No.	X_1-R1	LC/MS (M + H)+
47		544
48		468
49		482
50		496
51		510
52		494
53		592
54		530

Example 55

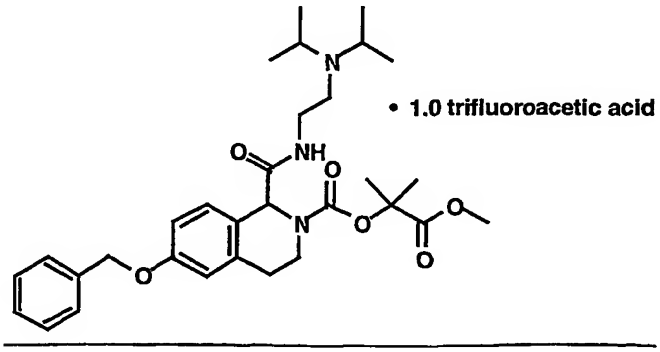


A.



To a -5°C solution of methyl 2-hydroxyisobutyrate (118 mg, 1.0 mmol) and triethylamine (139 µL, 1.0 mmol) in dichloromethane (4 mL) was added 1.9 M phosgene in toluene (0.8 mL, 1.5 mmol). After stirring for 1 h between -5 to 0°C, the reaction mixture was concentrated and used in the next procedure without purification.

B.

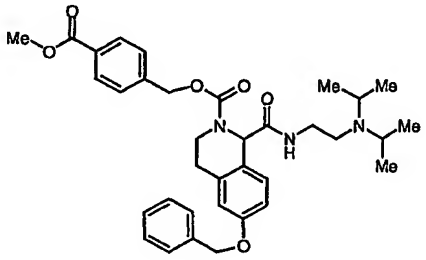
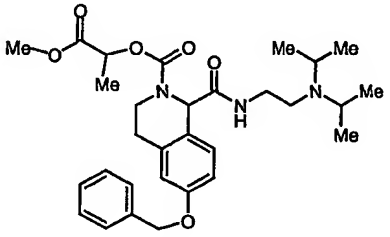
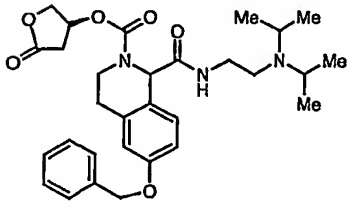
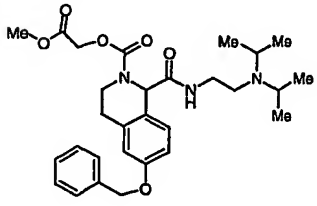


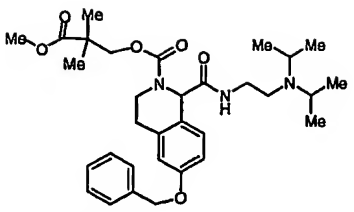
At 0°C, a solution of Part A compound (1.0 mmol) in dichloromethane (5 mL) was treated with Part A compound from Example 46 (45 mg, 0.11 mmol) followed by triethylamine (111 µL, 0.80 mmol). The reaction mixture was stirred at 0°C to 5°C for 2 h and then concentrated.

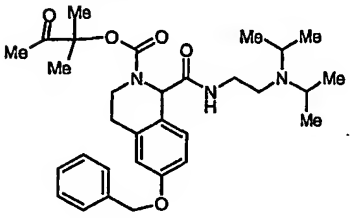
Purification by preparative HPLC, eluting with a gradient system of 30-100% B (where A = 90% water, 10% methanol, 0.2% trifluoroacetic acid and B = 90% methanol, 10% water, 0.2% trifluoroacetic acid), gave the title compound (52.2 mg, 71%) as a yellow oil: HPLCa rt = 3.81 min; LC/MS (electrospray, + ions) m/z 554(M+H).

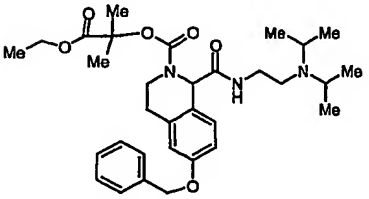
Examples 56 to 62

In a manner analogous to that of Example 55, Examples 56-62 compounds listed in the table below were prepared from Part A compound from Example 46 and the respective chloroformate prepared as in Example 55 Part A.

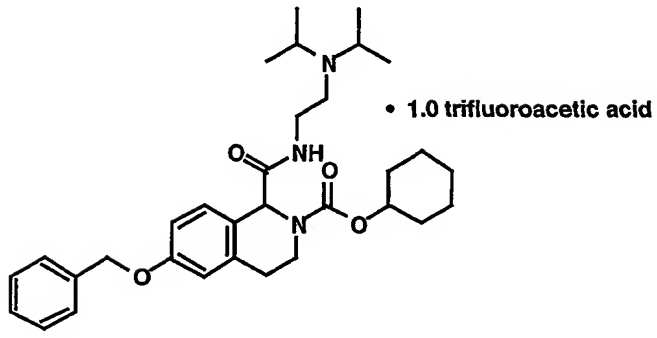
Example No.	Structure	LC/MS (M + H)+
56		602
57		540
58		538
59		526

60  568

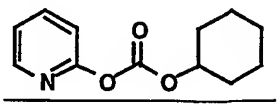
61  538

62  568

Example 63



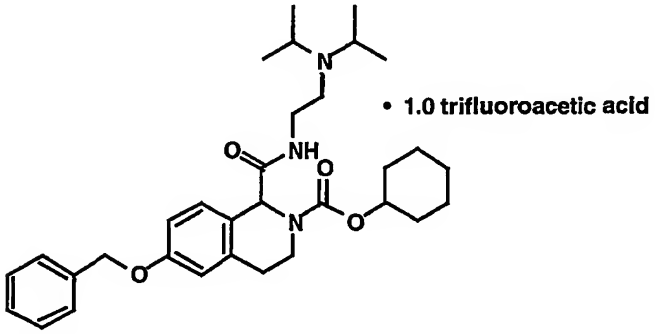
A.



A mixture of cyclohexanol (12.5 µL, 0.12 mmol), carbonic acid di-2-pyridyl ester (25.9 mg, 0.12 mmol) and triethylamine (16.7 µL, 0.12 mmol) in dichloromethane (5 mL) was stirred at ambient temperature overnight. The reaction mixture was concentrated, and the residue was partitioned between ethyl acetate (20 mL) and concentrated sodium carbonate solution. The two layers

were separated, and the organic layer was washed with brine and dried over magnesium sulfate. The mixture was filtered, and the filtrate was concentrated. The title product was purified by silica gel preparative TLC, eluting with 1:1 dichloromethane/ethyl acetate, and isolated in a yield of 26 mg (98%).

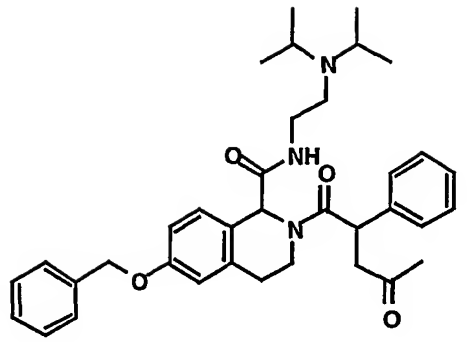
B.



To a solution of Part A compound from Example 46 (81.8 mg, 0.20 mmol) and triethylamine (27.8 µL, 0.20 mmol) in dichloromethane (7 mL) was added Part A compound (26 mg, 0.12 mmol). The reaction mixture was stirred at ambient temperature under nitrogen for 12 h. The mixture was purified by a SCX column as follows. The column was conditioned by rinsing with methanol (10 mL). The reaction mixture was loaded onto the column, followed by methanol (2 x 20 mL) and finally, the product was eluted with 2 N ammonia in methanol (6 mL). Further purification by preparative HPLC, eluting with 30-100% B (where A = 90% water, 10% methanol, 0.2% trifluoroacetic acid and B = 90% methanol, 10% water, 0.2% trifluoroacetic acid), gave the title compound (49.7 mg, 65%) as a yellow oil: LC/MS (electrospray, + ions) m/z 536(M+H).

Example 64

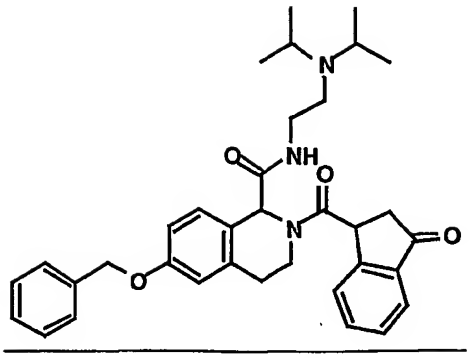
Isomer A and Isomer B



A solution of Part A compound from Example 46 (41.0 mg, 0.1 mmol) in dichloromethane (0.5 mL) was added to 2-phenyllevulinic acid (57.7 mg, 0.3 mmol) in a test tube. To the resultant mixture was added a solution of 1-hydroxybenzotriazole hydrate (33.8 mg, 0.25 mmol) in tetrahydrofuran (0.75 mL) followed by 1,3-diisopropylcarbodiimide (31.6 mg, 0.25 mmol). The reaction was stirred overnight. Methanol (3 mL) was added to ensure the reaction mixture was homogeneous. The mixture was purified by a SCX column as follows. The column was conditioned by rinsing with methanol (10 mL) and then pushing through air (10 mL). The reaction mixture was loaded onto the column. Air (10 mL) was pushed through the column followed by methanol (2 x 20 mL) and air (10 mL). Finally, the product was eluted with 2 N ammonia in methanol (6 mL) followed by air (10 mL). The solvent was removed from the sample by the use of a speed vacuum to give the two isomers of the title compound (56.5 mg, 97%) as an oil: HPLCb rt = 3.73 and 3.92 LC/MS (electrospray, + ions) m/z 584(M+H).

Example 65

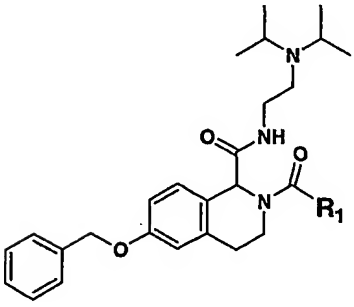
Isomer A and Isomer B



In a manner analogous to that of Example 64, the two isomers of the title compound were prepared from Part A compound from Example 46 (41.0 mg, 0.1 mmol) and 3-oxo-1-indancarboxylic acid (52.9 mg, 0.3 mmol) in yield of 55.2 mg (97%) as an oil: HPLCb rt = 3.45 and 3.51 min; LC/MS (electrospray, + ions) m/z 568(M+H).

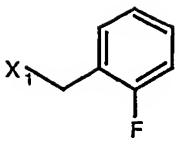
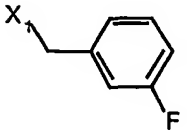
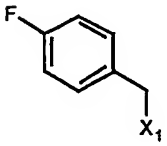
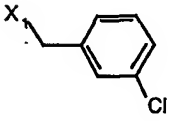
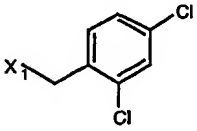
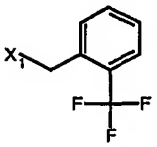
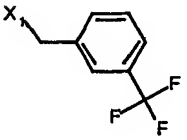
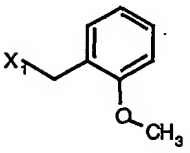
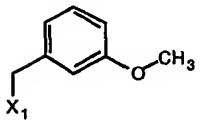
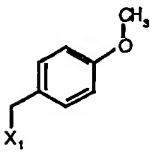
Examples 66 to 200

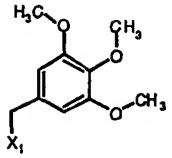
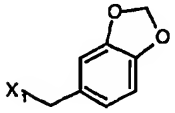
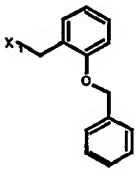
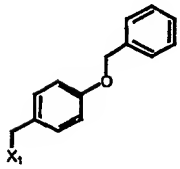
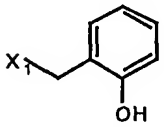
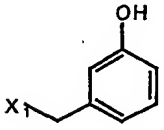
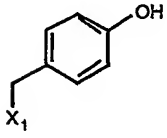
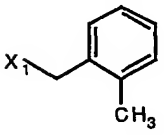
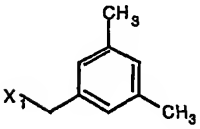
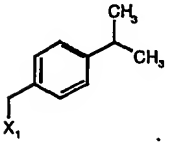
In a manner analogous to that of Examples 64 and 65, Examples 66-200 listed in the table below were prepared from Part A compound from Example 46 (0.1 mmol) and the respective carboxylic acid (0.3 mmol). A few compounds were purified by preparative HPLC, eluting with a gradient system of methanol and water with 0.2% trifluoroacetic acid. These compounds were isolated as trifluoroacetic acid salts.

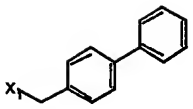
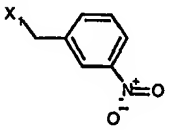
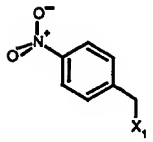
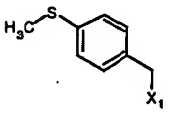
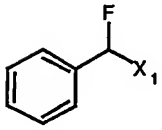
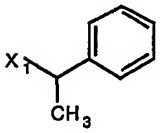
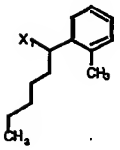
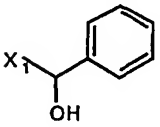
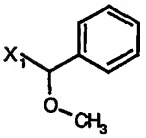
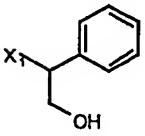


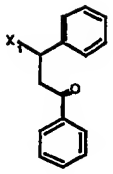
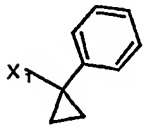
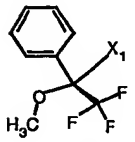
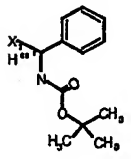
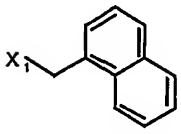
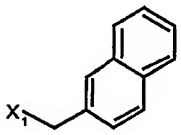
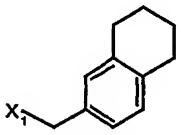
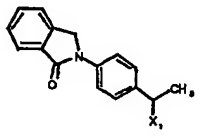
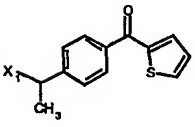
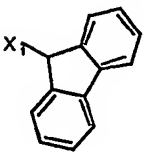
= X_1-R1

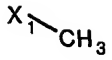
Example No.	X_1-R1	LC/MS (M + H)+

66		546
67		546
68		546
69		562
70		597
71		596
72		596
73		558
74		558
75		558

76		618
77		572
78		634
79		634
80		544
81		544
82		544
83		542
84		556
85		570

86		604
87		573
88		573
89		574
90		546
91		542
92		612
93		544
94		558
95		558

96		646
97		554
98		626
99		643
100		578
101		578
102		582
103		673
104		652
105		602

106		452
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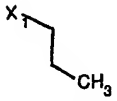
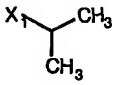
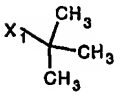
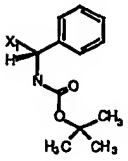
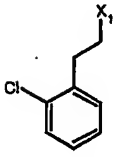
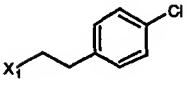
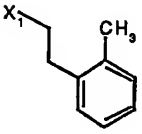
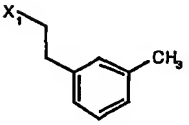
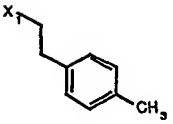
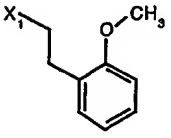
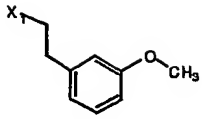
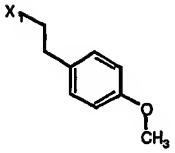
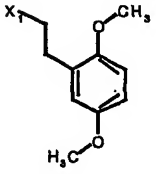
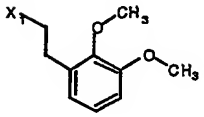
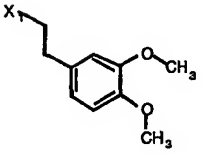
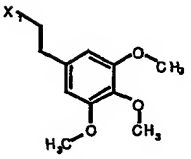
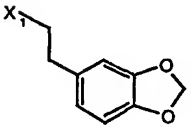
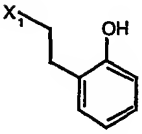
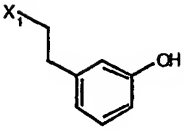
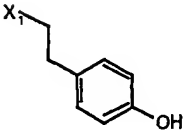
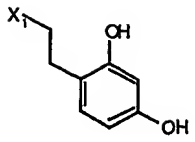
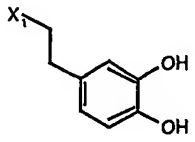
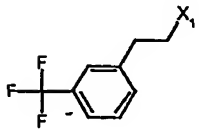
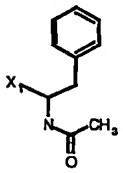
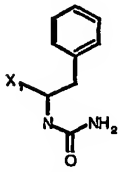
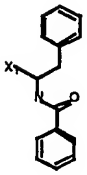
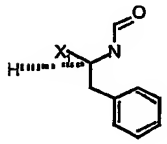
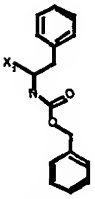
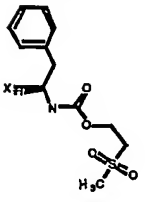
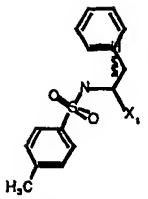
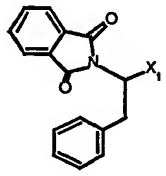
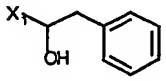
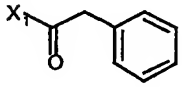
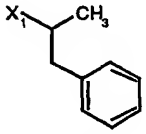
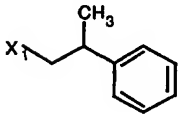
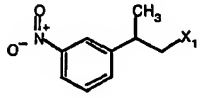
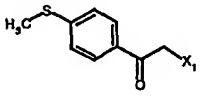
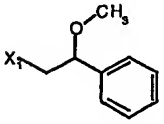
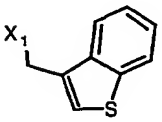
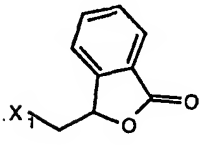
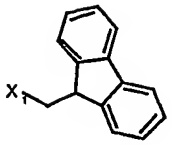
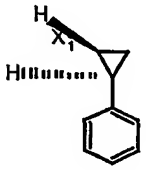
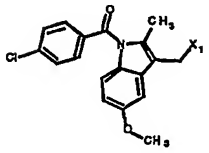
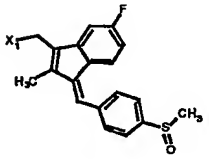
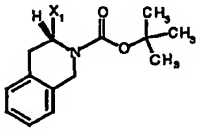
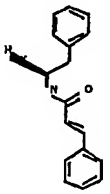
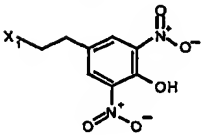
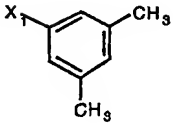
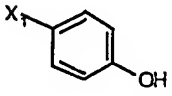
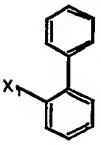
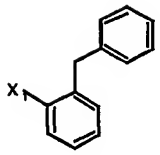
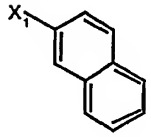
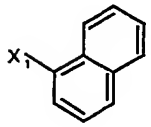
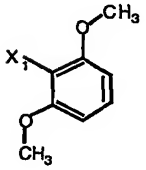
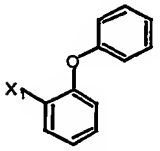
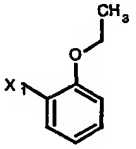
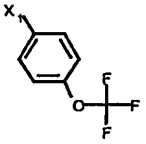
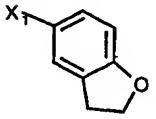
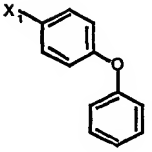
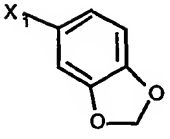
108		480
109		480
110		494
111		643
112		576
113		576
114		556
115		556
116		556
117		572

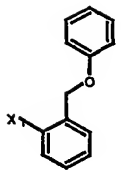
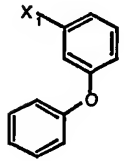
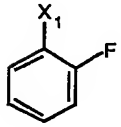
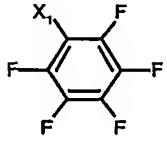
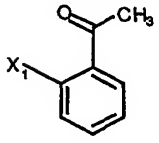
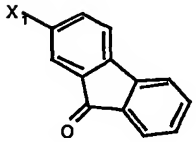
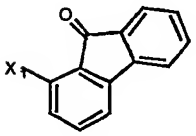
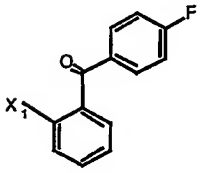
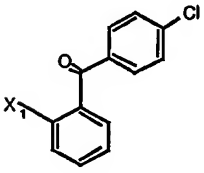
118		572
119		572
120		602
121		602
122		602
123		632
124		586
125		558
126		558
127		558

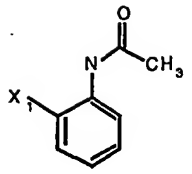
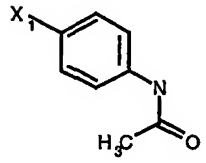
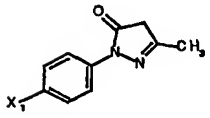
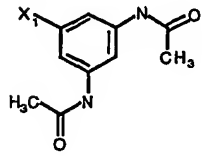
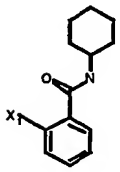
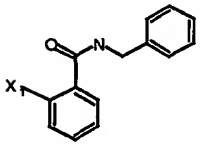
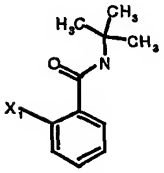
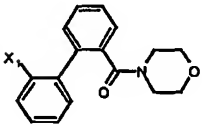
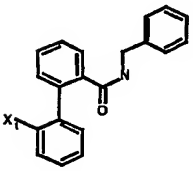
128		574
129		574
130		610
131		599
132		600
133		661
134		585
135		691
136		707

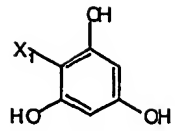
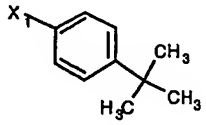
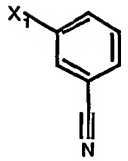
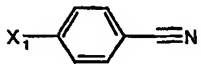
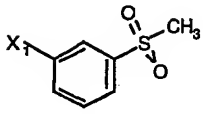
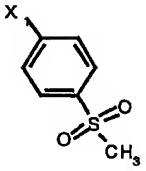
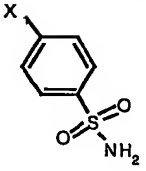
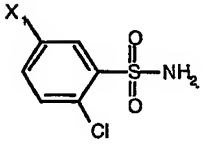
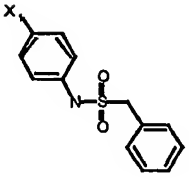
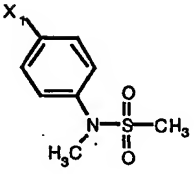
137		711
138		687
139		558
140		556
141		556
142		556
143		601
144		602
145		572
146		584
147		584

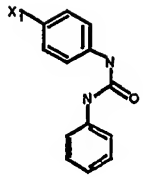
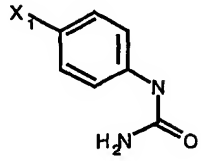
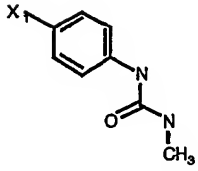
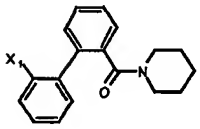
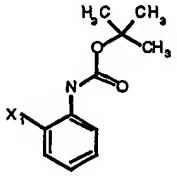
148		616
149		554
150		749
151		748
152		669
153		687
154		648
155		542
156		530
157		590

158		604
159		564
160		564
161		574
162		606
163		558
164		598
165		556
166		606
167		558

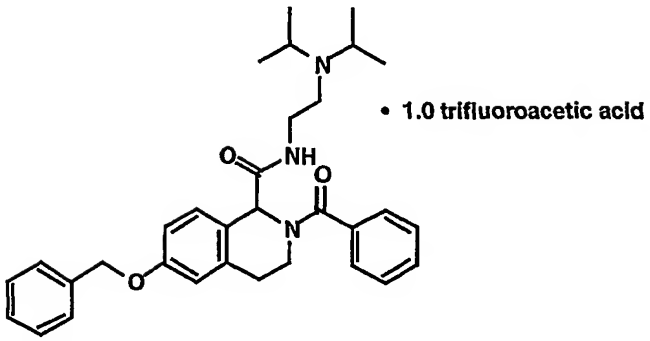
168		620
169		606
170		532
171		604
172		556
173		616
174		616
175		636
176		652

177		571
178		571
179		610
180		628
181		639
182		647
183		613
184		703
185		723

186		562
187		570
188		539
189		539
190		592
191		592
192		593
193		627
194		683
195		621

196		648
197		572
198		586
199		701
200		629

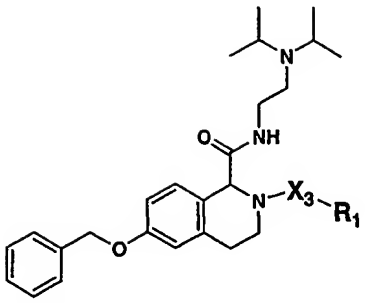
Example 201



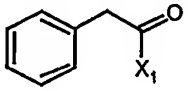
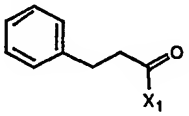
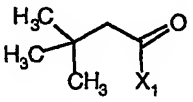
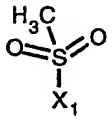
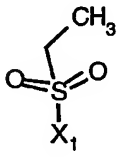
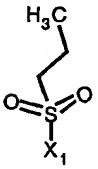
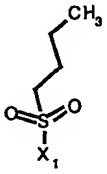
To a 0°C solution of benzoyl chloride (28.1 mg, 0.2 mmol) in dichloromethane (0.5 mL) was added Part A compound from Example 46 (61 mg, 0.15 mmol) followed by triethylamine (27 µL, 0.19 mmol). The reaction mixture was stirred at ambient temperature under nitrogen overnight and then was concentrated. The residue was partitioned between ethyl acetate and water. The two layers were separated, and the ethyl acetate layer was concentrated. Purification by preparative HPLC, eluting with 30-100% B (where A = 90% water, 10% methanol, 0.2% trifluoroacetic acid and B = 90% methanol, 10% water, 0.2% trifluoroacetic acid), gave the title compound (61.5 mg, 66%) as a pale yellow semi-solid/oil: LC/MS (electrospray, + ions) m/z 514 (M+H).

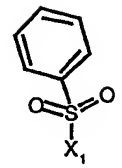
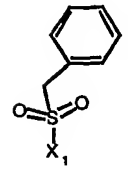
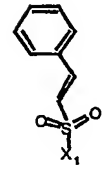
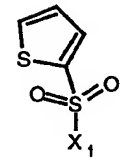
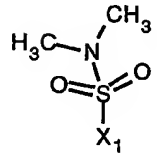
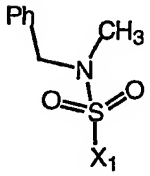
Examples 202 to 214

In a manner analogous to that of Example 201, Examples 202-214 in the table below were prepared from Part A compound from Example 46 and the respective acid chloride, sulfonyl chloride, sulfamoyl chloride.



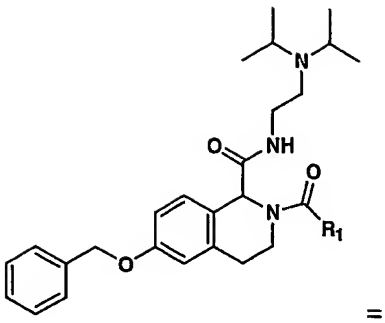
= X_1-X3-R1

Example No.	X_1-X3-R1	LC/MS (M + H)+
202		528
203		542
204		508
205		488
206		502
207		516
208		530

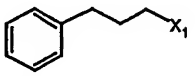
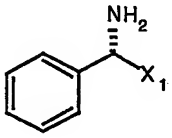
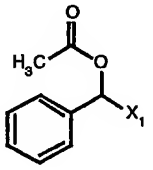
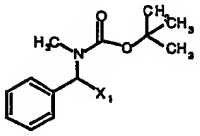
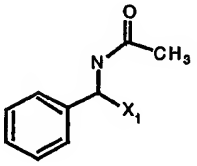
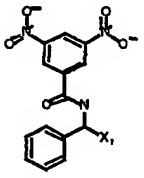
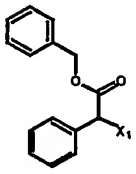
209		550
210		564
211		576
212		556
213		517
214		593

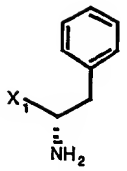
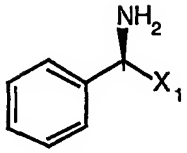
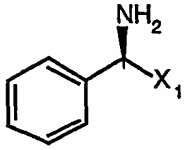
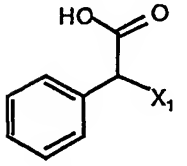
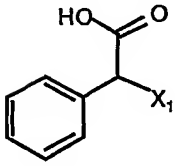
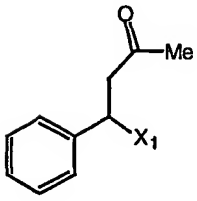
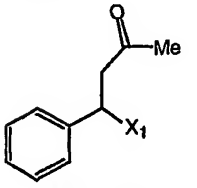
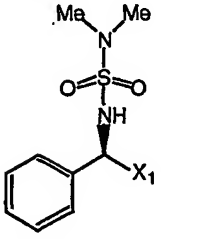
Examples 215 to 229

Examples 215-229 were prepared by methods described in earlier examples and by methods known in the art starting from Part A compound from Example 46 and the corresponding carboxylic acid.

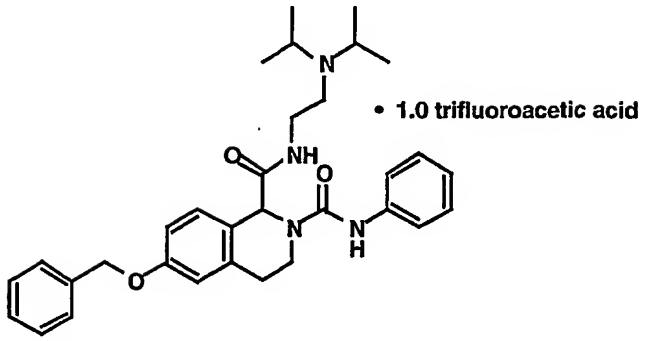


= X_1-R1

Example No.	X_1-R1	LC/MS $(M + H)^+$
215		556
216		543
217		586
218		657
219		585
220		737
221		662

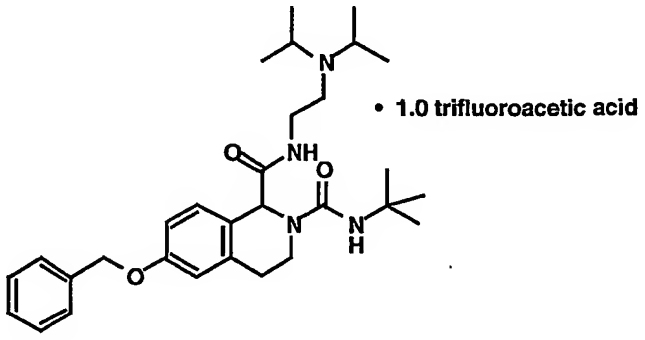
222		557
223		543
224		543
225		572
226		572
227 Isomer A		584
228 Isomer B		584
229		650

Example 230



To a solution of Part A compound from Example 46 (61 mg, 0.15 mmol) in dichloromethane (0.5 mL) was added phenyl isocyanate (19.7 mg, 0.165 mmol) via a syringe. Additional dichloromethane (0.5 mL) was added. The reaction mixture was stirred overnight, and then it was concentrated. Purification on preparative HPLC, eluting with a gradient system of 30-100% B (where A = 90% water, 10% methanol, 0.2% trifluoroacetic acid and B = 90% methanol, 10% water, 0.2% trifluoroacetic acid), gave the title compound (81 mg, 85%) as a white foam: HPLCb rt = 3.70 min.; LC/MS (electrospray, + ions) m/z 529 (M+H).

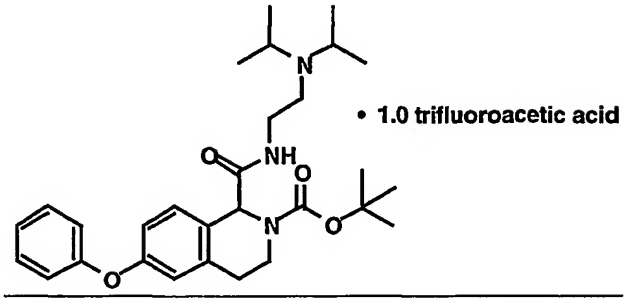
Example 231



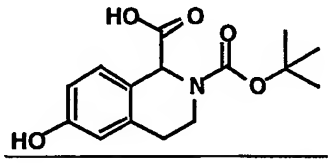
In a manner analogous to that of Example 230, the title compound was prepared from Part A compound from Example 46 (61 mg, 0.15 mmol) and *tert*-butyl isocyanate (16.4 mg, 0.165 mmol) in a yield of 69.5 mg (75%) as a

white semi-solid/oil: HPLCb rt = 3.71 min.; LC/MS (electrospray, + ions) m/z 509 (M+H).

Example 232

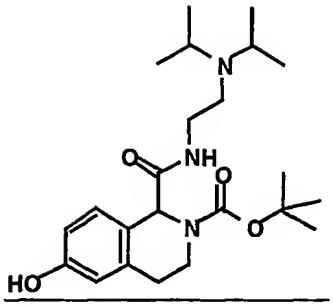


A.



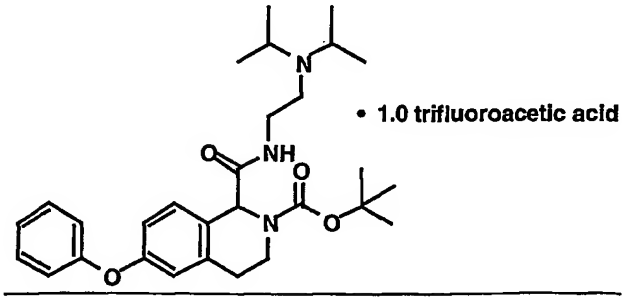
To a solution of Part C compound from Example 1 (1.00 g, 3.25 mmol) in methanol (1 mL) and tetrahydrofuran (1 mL) was added a solution of sodium hydroxide (260 mg, 6.5 mmol) in water (650 µL). The reaction was stirred overnight at ambient temperature, heated at 60°C for 6 h and then stirred at ambient temperature overnight. The solvent was removed *in vacuo*, and the residue was partitioned between water and ethyl acetate. The aqueous layer was separated and acidified with 6 N hydrochloric acid solution to pH ~3 and extracted with ethyl acetate (2x) The organic layers were dried over sodium sulfate and the mixture was filtered. The filtrate was concentrated to give the title compound (930 mg, 97.5%) as a clear oil, which became a white foam.

B.



To a solution of Part A compound (500 mg, 1.7 mmol) and diisopropylethylenediamine (326 µL, 1.9 mmol) in dimethylformamide (10 mL) was added diisopropylethylamine (890 µL, 5.1 mmol) followed by 1-hydroxy-7-azabenzotriazole (325 mg, 2.4 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (327 mg, 1.7 mmol). After stirring the reaction mixture overnight, the mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic layer was washed with water (2x) and brine, and then dried over sodium sulfate. The mixture was filtered and the filtrate concentrated *in vacuo* to give the title product (587 mg, 82.1%) as a white foam.

C.



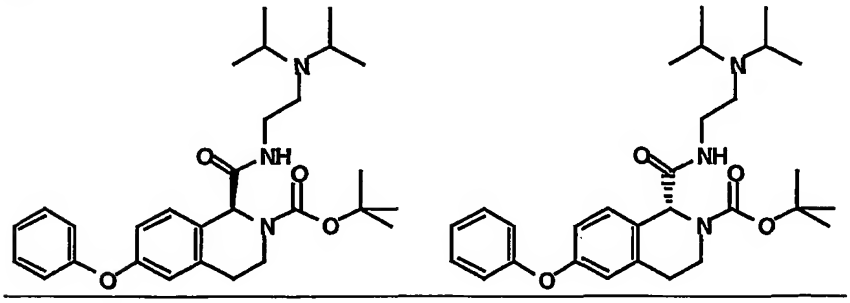
To a slurry of Part B compound (50 mg, 0.12 mmol), phenyl boronic acid (29 mg, 0.24 mmol), copper(II) acetate (22 mg, 0.12 mmol) and 4 Å powdered molecular sieves in dichloromethane (1.2 mL) was added pyridine (48 µL, 0.60 mmol). The reaction was stirred overnight and then was filtered. The filtrate was concentrated to a

green oil that was purified by preparative HPLC. The title compound (59 mg, 81%) was obtained as a yellow oil: : HPLCa1 rt = 2.2 min.; LC/MS (electrospray, + ions) m/z 496 (M+H).

Example 233

Isomer A and Isomer B

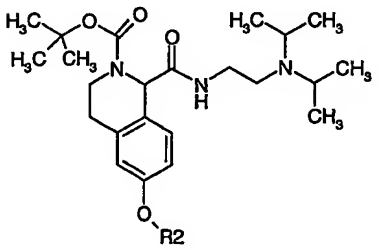
A.



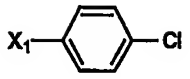
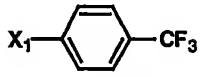
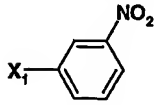
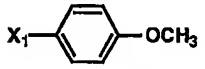
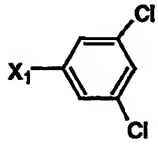
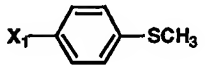
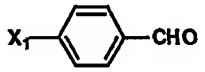
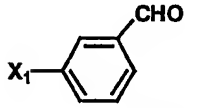
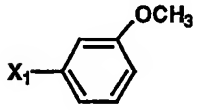
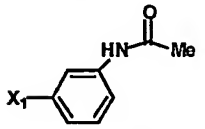
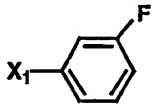
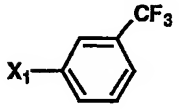
Title compound, Example 232 (70 mg) was resolved on Chiralpak AD column (50 x 500 mm), eluting with 20% isopropanol/hexanes to give the title compounds, Isomer A (28 mg) and Isomer B (30 mg).

Examples 234 to 245

In a manner analogous to that of Example 232, Examples 234-245 compounds listed in the table below were prepared from Part B compound from Example 232 (0.12 mmol) and the respective phenylboronic acid (0.24 mmol). A few compounds were purified by preparative HPLC, eluting with a gradient system of methanol and water with 0.2% trifluoroacetic acid. These compounds were isolated as trifluoroacetic acid salts.

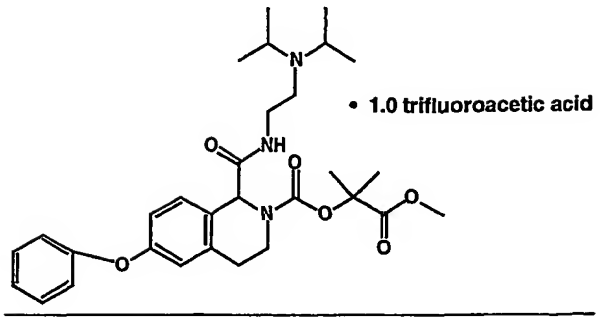


= X_1-R2

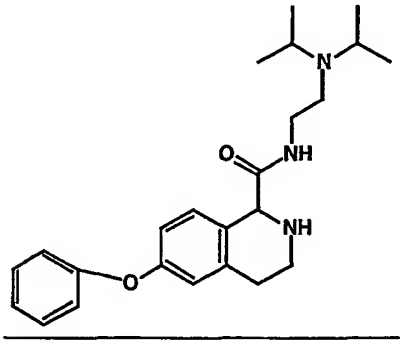
Example No.	X_1-R2	LC/MS (M + H)+
234		531
235		564
236		541
237		526
238		565
239		542
240		524
241		524
242		526
243		553
244		514
245		564

5

Example 246

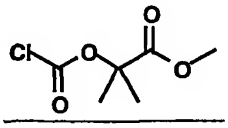


A.



To neat title compound from Example 232 (1.56 g, 3.15 mmol) is added 4N hydrogen chloride (7 mL, dioxane solution) at room temperature. After 3 h, the volatiles were removed in vacuo, the residue redissolved in ethyl acetate and the pH adjusted to 8 with 1N sodium hydroxide. The organic layer was dried and concentrated to give the title compound (1.11 g) as a yellow colored oil. LC/MS (electrospray, + ions) m/z 396(M+H).

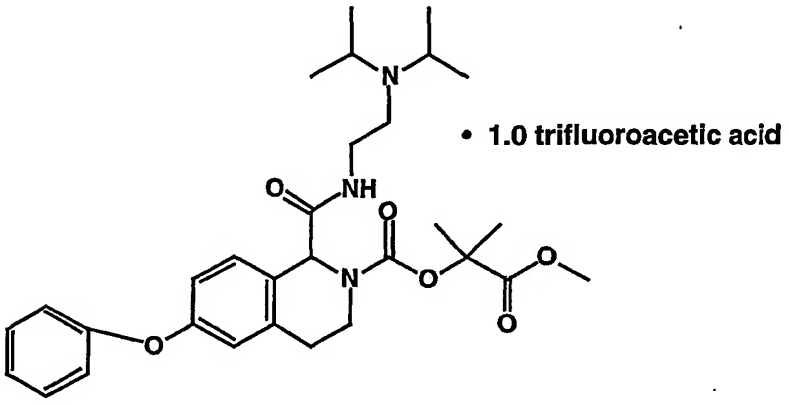
B.



To a 0°C solution of methyl 2-hydroxyisobutyrate (236 mg, 2.0 mmol) and triethylamine (202 mg, 2.0 mmol)

in tetrahydrofuran (5 mL) was added 1.9 M phosgene in toluene (1.68 mL, 3.2 mmol). After stirring for 2 h between -5 to 0°C, the reaction mixture was concentrated and used in the next procedure without purification.

C.

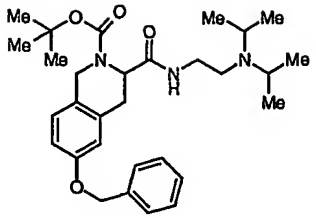
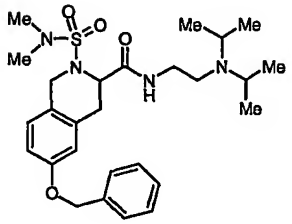
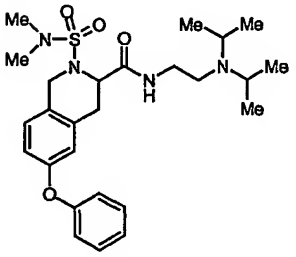


At 0°C, a solution of Part B compound (2.0 mmol) in dichloromethane (5 mL) was treated with Part A compound(118.9 mg, 0.30 mmol) followed by triethylamine (101.2 mg, 1.0 mmol). The reaction mixture was stirred at 0°C to 5°C for 2 h and then concentrated. Purification by preparative HPLC, eluting with a gradient system of 40-100% B (where A = 90% water, 10% methanol, 0.2% trifluoroacetic acid and B = 90% methanol, 10% water, 0.2% trifluoroacetic acid), gave the title compound (115.8 mg) as a yellow oil; LC/MS (electrospray, + ions) m/z 540(M+H).

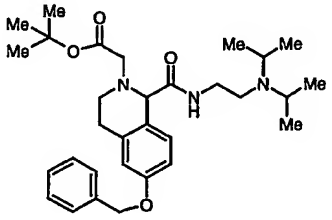
Examples 247 to 250

Examples 247-250 listed below can were prepared as shown in Scheme 11 and employing the procedures described above, the working examples, and methods known in the arts.

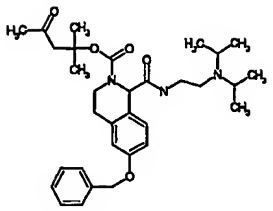
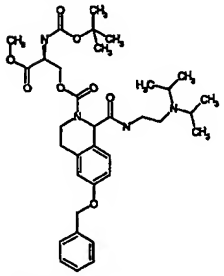
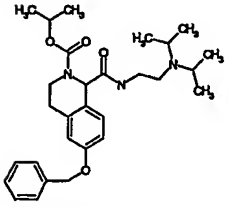
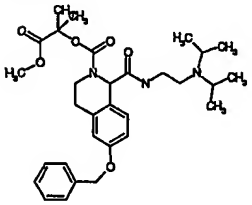
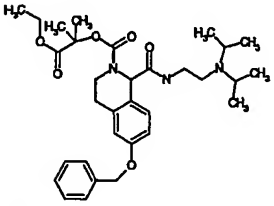
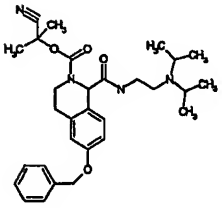
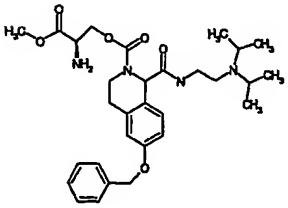
Example No.	Structure	LC/MS (M + H)+

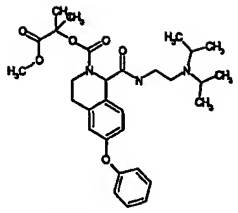
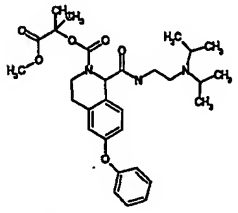
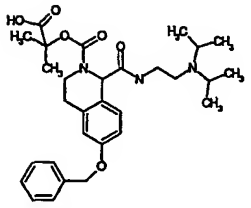
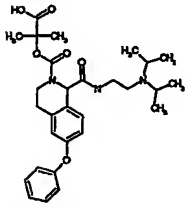
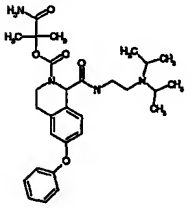
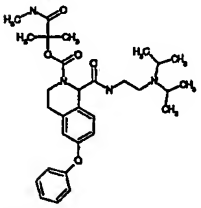
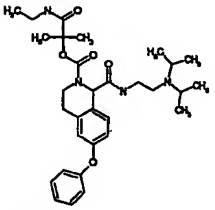
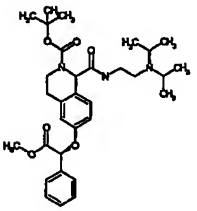
247		510
248		517
249		503

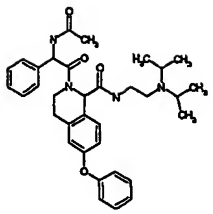
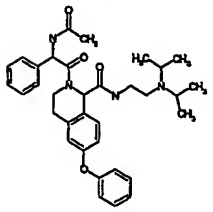
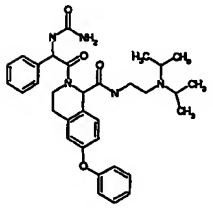
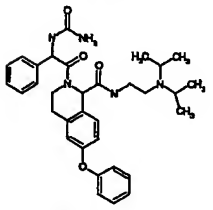
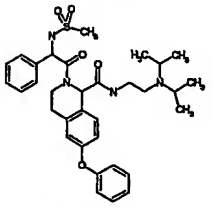
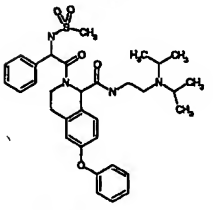
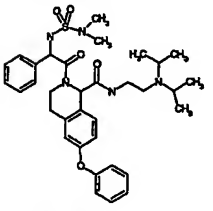
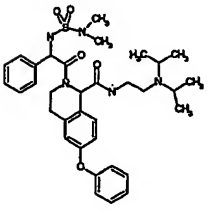
Examples listed below can be prepared from intermediate Part A compound from Example 46 and an alkyl halide:

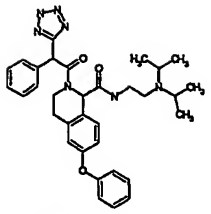
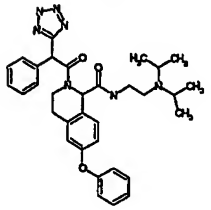
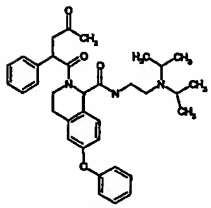
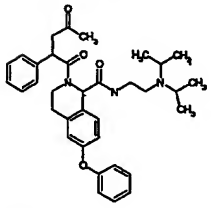
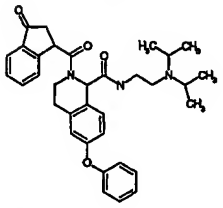
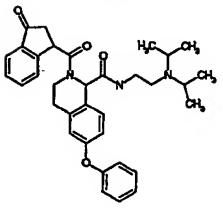
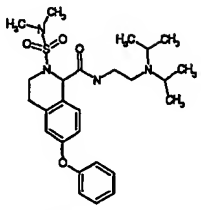
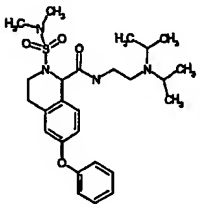
Example No.	Structure	LC/MS (M + H)+
250		524

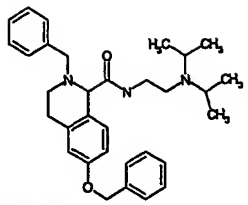
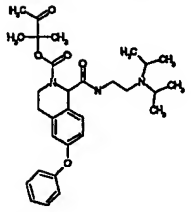
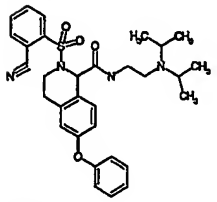
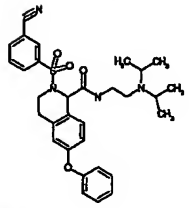
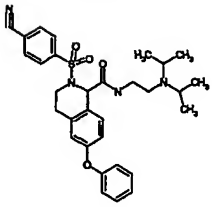
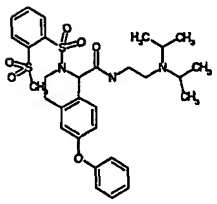
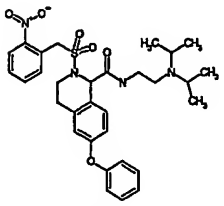
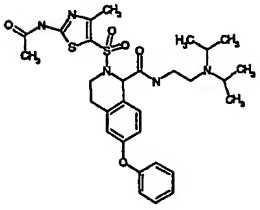
Examples listed in the Table below can be prepared employing the procedures described above, the working examples, and methods known in the arts.

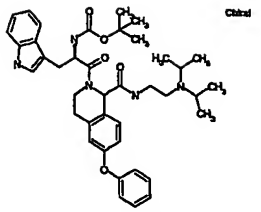
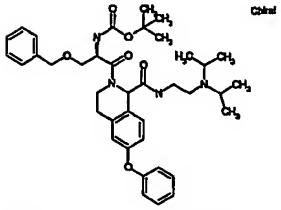
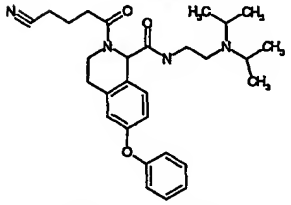
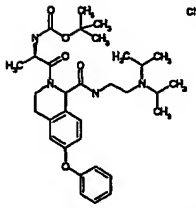
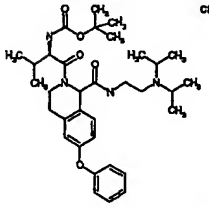
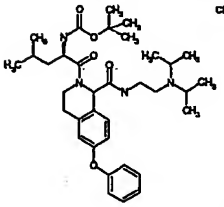
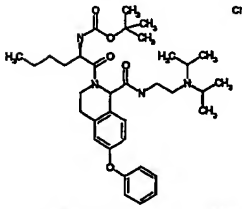
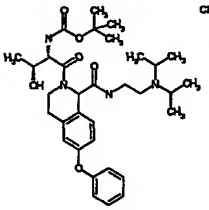
Example No.	Structure	LC/MS (M+H)+
251		552
252		655
253		496
254		554
255		568
256		521
257		555

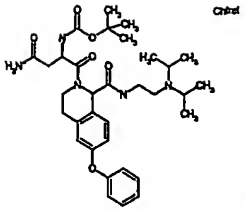
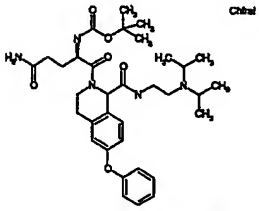
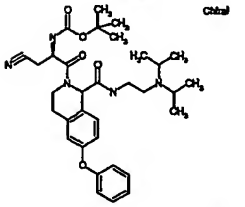
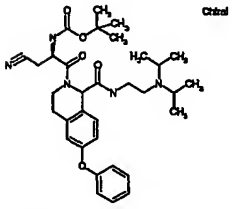
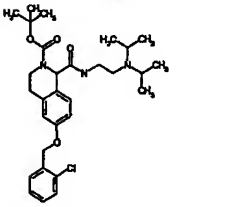
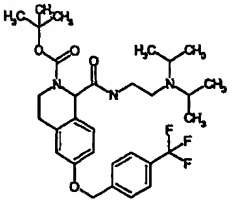
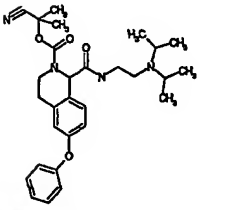
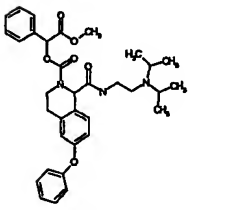
258 Isomer A		540
259 Isomer B		540
260		540
261		526
262		525
263		539
264		553
265		568

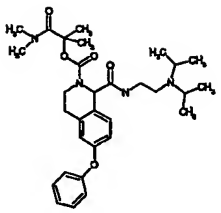
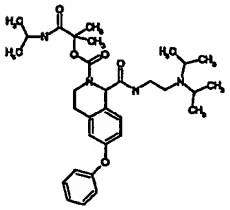
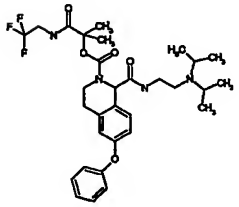
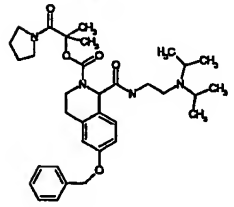
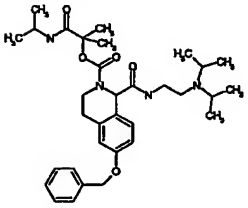
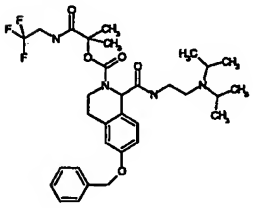
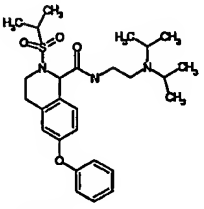
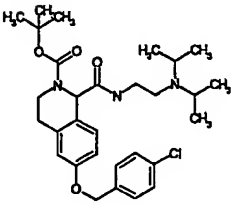
266 Diastereomer A		571
267 Diastereomer B		571
268 Diastereomer A		572
269 Diastereomer B		572
270 Diastereomer A		607
271 Diastereomer B		607
272 Diastereomer A		636
273 Diastereomer B		636

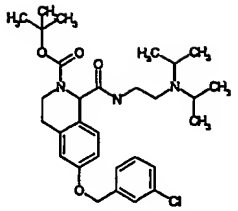
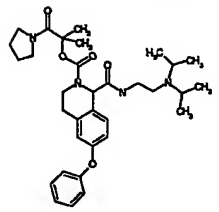
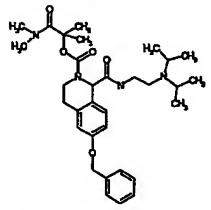
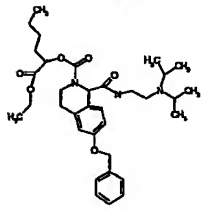
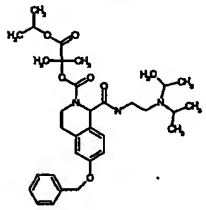
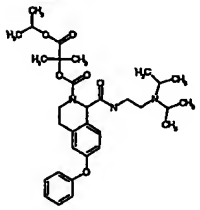
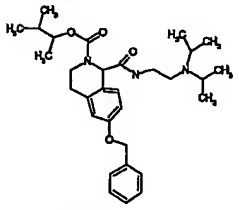
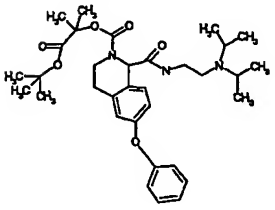
274 Diastereomer A		582
275 Diastereomer B		582
276 Diastereomer A		570
277 Diastereomer B		570
278 Diastereomer A		554
279 Diastereomer B		554
280 Isomer A		503
281 Isomer B		503

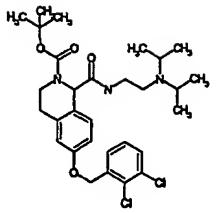
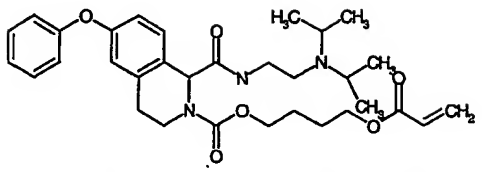
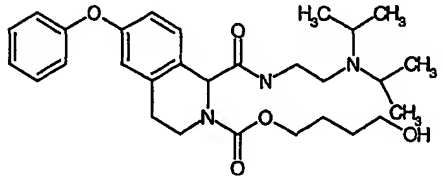
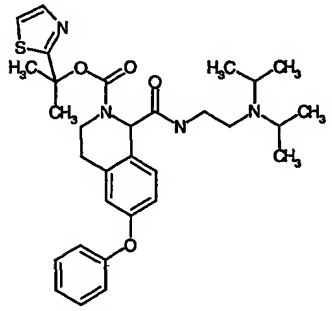
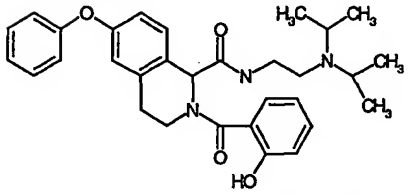
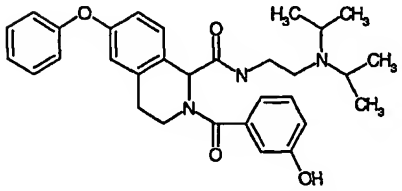
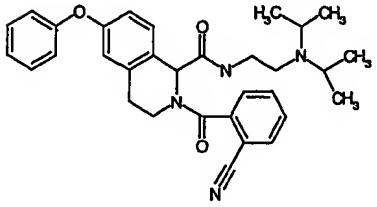
282		500
283		524
284		561
285		561
286		561
287		614
288		595
289		614

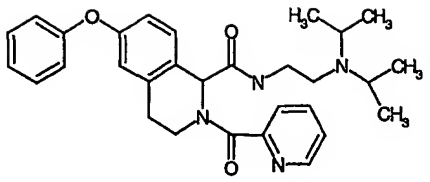
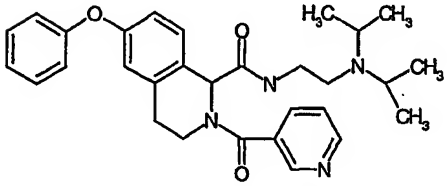
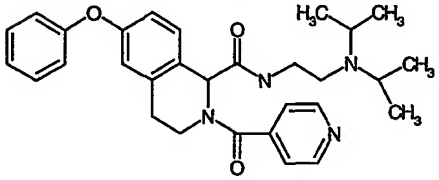
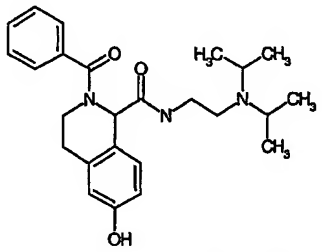
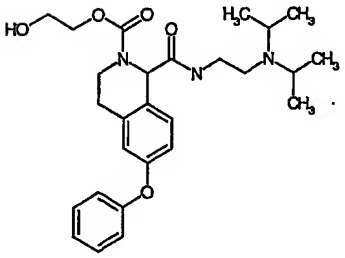
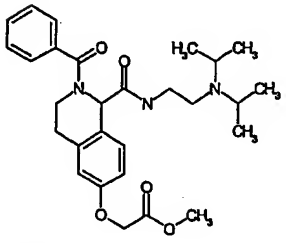
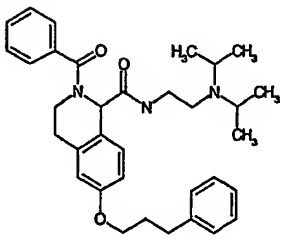
290		682
291		673
292		491
293		567
294		595
295		609
296		609
297		597

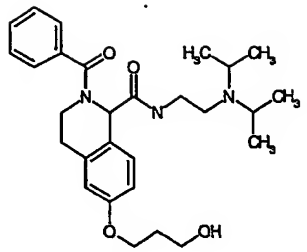
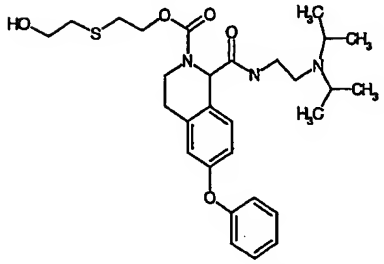
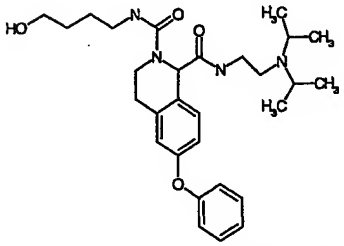
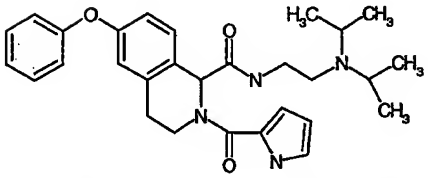
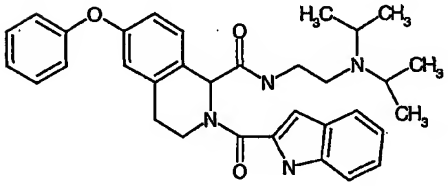
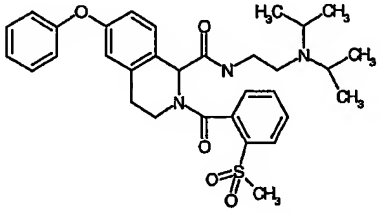
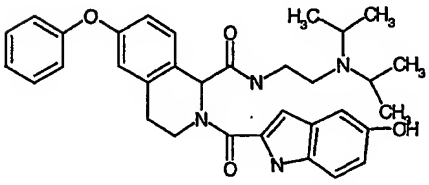
298		610
299		624
300		592
301		592
302		545
303		578
304		507
305		588

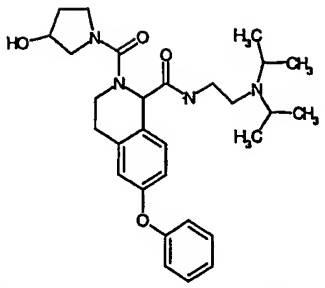
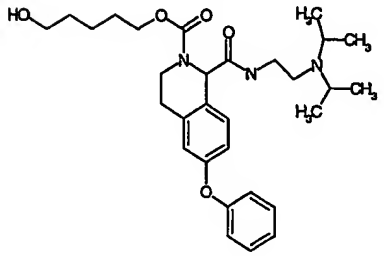
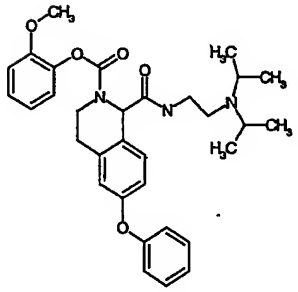
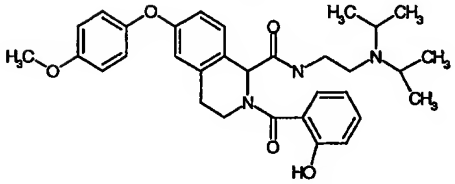
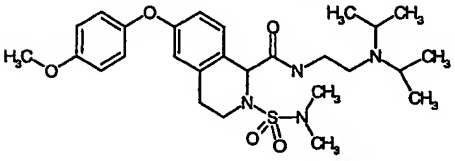
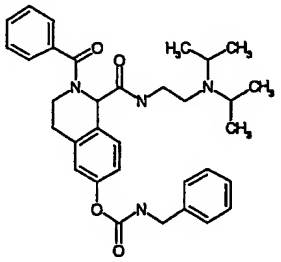
306		553
307		567
308		607
309		593
310		581
311		621
312		502
313		545

314		545
315		579
316		567
317		596
318		582
319		568
320		524
321		582

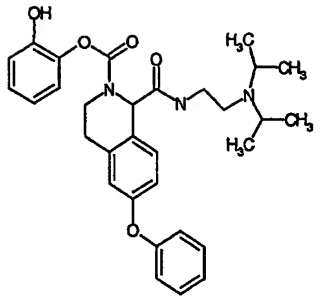
322		579
323		566
324		512
325		565
326		516
327		516
328		525

329		501
330		501
331		501
332		424
333		484
334		496
335		542

336		482
337		544
338		511
339		489
340		539
341		587
342		555

343		509
344		526
345		546
346		546
347		533
348		557

349



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We claim:

1. A compound which has the structure

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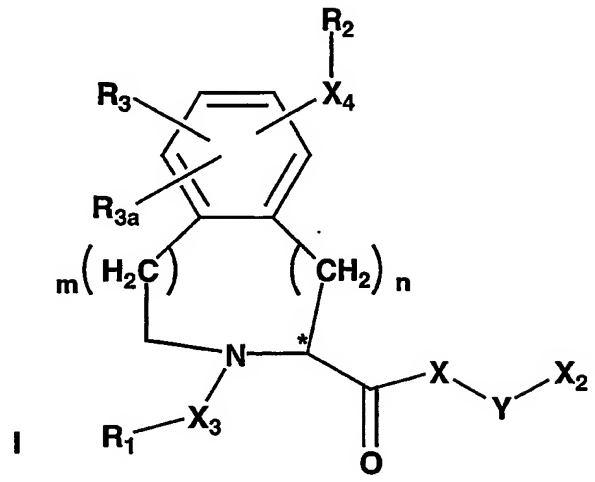


I

pharmaceutically acceptable salts, prodrug esters, and all stereoisomers thereof wherein

R_1 is alkyl, aryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, cycloalkyl, cycloalkylalkyl, cycloalkyl-alkoxy, alkoxyalkyl, alkylthioalkyl, aryloxyalkyl, arylalkoxyalkyl, cyclohetero-alkyl, cycloheteroalkylalkyl, heteroaryl, or heteroaryl-alkyl, and where these groups may be optionally substituted with 1 to 3 J1 groups which may be the same or different and the R_1 aryls may be further optionally substituted with 1 to 5 halogens, aryl, $-CF_3$, $-OCF_3$, 1-3 hydroxyls, 2 of which substituents where possible, may be joined by a methylene bridge;

R_2 is H, alkyl, aryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, aryloxyalkyl, arylalkoxyalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkylalkoxy, heteroaryl, or heteroarylalkyl, and where these groups may be optionally substituted with a J1a group and the aryls may be further

optionally substituted with 1 to 5 halogens, $-CF_3$, $-OCF_3$, or 1-3 hydroxyls;

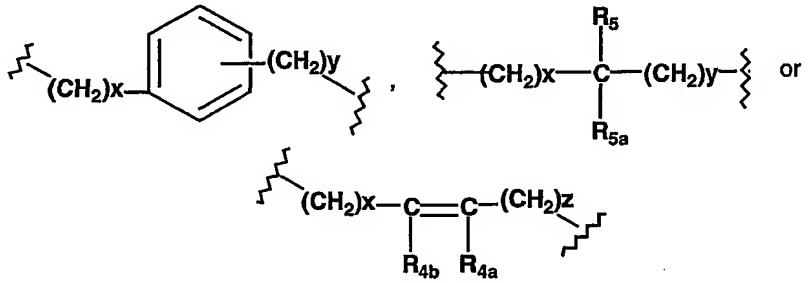
X is a bond, -O-, or $-NR_4-$;

R_3 and R_{3a} are the same or different and are independently selected from H, alkoxy, halogen, $-CF_3$, alkyl, or aryl;

R_4, R_{4a}, R_{4b}, R_{4c}, R_{4d}, R_{4e}, R_{4f}, R_{4g}, R_{4h}, R_{4i}, R_{4j}, R_{4k}, and R_{4l} are the same or different and are independently selected from H, C_1-C_6alkyl, or aryl;

m and n are the same or different and are independently 0 or 1;

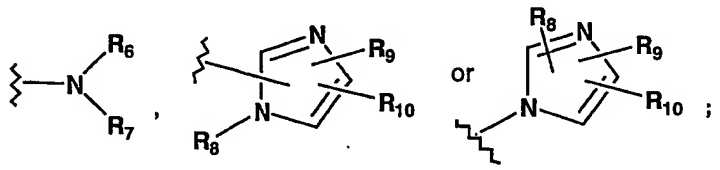
Y is



where x and y are the same or different and are independently 0 to 3 and z is 1 to 3;

R_5 and R_{5a} are the same or different and are independently H, alkyl, alkoxy, hydroxyl, halogen, $-CF_3$, aryl, alkaryl, and cycloalkyl; or R_5 and R_{5a} can be independently joined to one or both of R_6 and R_7 groups to form an alkylene bridge of 1 to 5 carbon atoms; or R_5 and R_{5a} can be joined together to form a ring of from 4-7 carbon atoms;

X_2 is



R_6 and R_7 are the same or different and are independently selected from H and alkyl, where the alkyl may be

optionally substituted with halogen, 1 to 3 hydroxyls, 1 to 3 C_1-C_{10}alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, C_1-C_6alkoxycarbonyl; or R_6 and R_7 can together form $-(CH_2)_tX_5(CH_2)_u-$ where X_5 is $-C(R_{4c})(R_{4d})-$, $-O-$ or $-N(R_{4e})-$, t and u are the same or different and are independently 1-3;

R_8 is H, C_1-C_6alkyl, $-CF_3$, alkaryl, or aryl, and with the alkyl and aryl groups being optionally substituted with 1 to 3 hydroxyls, 1 to 3 C_1-C_{10}alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy or C_1-C_6 alkoxycarbonyl;

R_9 and R_{10} are the same or different and are independently selected from H, C_1-C_6alkyl, $-CF_3$, alkaryl, aryl, or halogen, and with the alkyl and aryl groups being optionally substituted with 1 to 3 hydroxyls, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy or C_1-C_6 alkoxycarbonyl;

X_3 is a bond, $-C(O)-$, $-C(O)O-$, $-C(O)\ N(R_{4f})-$, $-S(O)_2-$, or $-S(O)_2N(R_{4f})-$;

X_4 is a bond, $-O-$, $-OC(O)-$, $-N(R_{4g})-$, $-N(R_{4g})C(O)-$, $-N(R_{4g})C(O)N(R_{4h})-$, $-N(R_{4g})S(O)_2-$, $-N(R_{4g})S(O)_2N(R_{4h})$, $-OC(O)N(R_{4g})-$, $-C(O)-$, $-C(O)N(R_{4g})-$, $-S-$, $-S(O)_2-$, or $-S(O)_2N(R_{4g})-$;

J1 and J1a are the same or different and are independently nitro, halogen, hydroxyl, $-OCF_3$, $-CF_3$, alkyl, $-(CH_2)vCN$, $-(CH_2)_vN(T_{1a})C(O)T_1$, $-(CH_2)_vN(T_{1a})C(O)OT_1$, $-(CH_2)_vN(T_{1a})C(O)N(T_{1b})T_1$, $-(CH_2)_vNT_1(T_{1a})$, $-(CH_2)_vN(T_{1a})SO_2T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOC(O)OT_1$, $-(CH_2)_vOC(O)T_1$, $-(CH_2)_vOC(O)OT_1$, $-(CH_2)_vOC(O)T_1$, $-(CH_2)_vOC(O)N(T_{1a})T_1$, $-(CH_2)_vN(T_{1a})SO_2N(T_{1a})T_1$, $-(CH_2)_vOT_1$, $-(CH_2)_vSO_2T_1$, $-(CH_2)_vSO_2N(T_{1b})T_1$, $-(CH_2)_vC(O)T_1$, $-(CH_2)_vCH(OH)T_1$, or heteroaryl as defined below, with v being 0-3;

T_1, T_{1a} and T_{1b} are the same or different and are independently H, alkyl, alkenyl, alkynyl, lower alkythioalkyl, alkoxyalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, or

cycloalkyl, each of which may be optionally substituted with halogen, hydroxyl, $-C(O)NR_{4i}R_{4j}$, $-NR_{4i}C(O)R_{4j}$, -CN, $-N(R_{4i})SO_2R_{11}$, $-OC(O)R_{4i}$, $-SO_2NR_{4i}R_{4j}$, $-SOR_{11}$, $-SO_2R_{11}$, alkoxy, -COOH, cycloheteroalkyl, or $-C(O)OR_{11}$; with the proviso that T_1 cannot be hydrogen when it is connected to sulfur as in SO_2T_1;

or T_1 and T_{1a} or T_1 and T_{1b} can together form $-(CH_2)_rX_{5a}(CH_2)_s-$ where X_{5a} is $-C(R_{4k})(R_{4l})-$, -O- or $-N(R_{4k})-$, where r and s are the same or different and are independently 1-3;

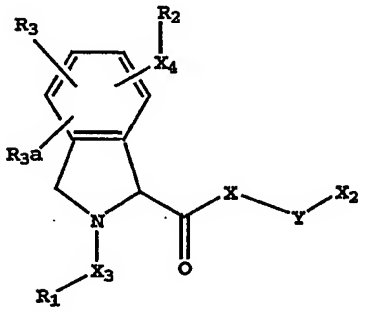
R_{11} is C_1-C_6alkyl or aryl;

provided

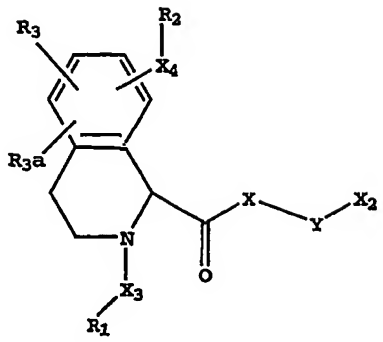
(1) where m is 0 and n is 1, the moiety $-X_4-R_2$ is other than alkyl or alkoxy; and

(2) where X is a bond and X_2 is amino, then m is 1.

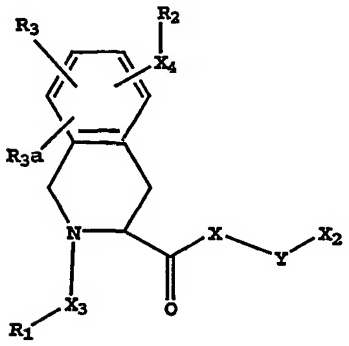
2. The compound as defined in Claim 1 having the structure



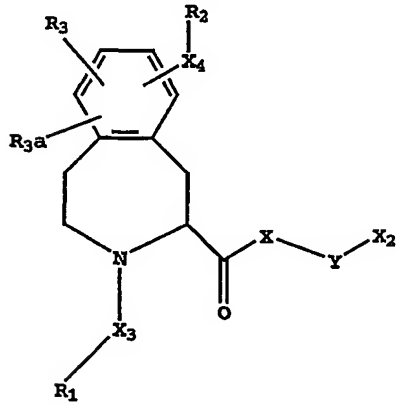
3. The compound as defined in Claim 1 having the structure



4. The compound as defined in Claim 1 having the following structure:



5. The compound as defined in Claim 1 having the following structure:



6. The compound as defined in Claim 1 wherein

R_1 is alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, aryloxyalkyl, heteroaryl, or heteroarylalkyl, any of which may be optionally substituted with a J1 group;

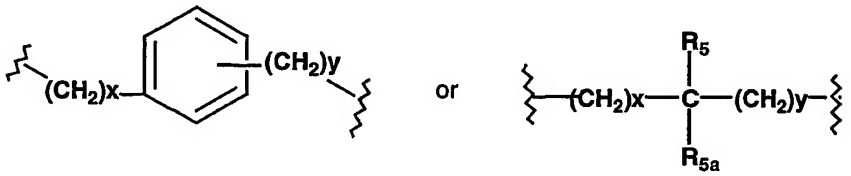
R_2 is alkyl, aryl, arylalkyl, alkoxyalkyl, aryloxyalkyl, heteroaryl, cycloalkyl, cycloalkylalkyl, or heteroarylalkyl, and these groups may be optionally substituted by J1a;

R_3 and R_{3a} are the same or different and are independently selected from H, alkoxy, halogen, or $-CF_3$;

m and n are independently 0 or 1;

X is O or $-NR_4-$;

Y is

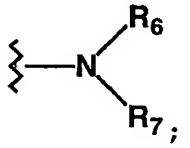


where x and y are independently 0 to 3;

R_4 is H or C_1-C_6 alkyl;

R_5 and R_{5a} are the same or different and are independently selected from H, alkyl, or $-CF_3$, or R_5 and R_{5a} can be independently joined to one or both of R_6 and R_7 groups to form an alkylene bridge of 1 to 5 carbon atoms;

X_2 is



R_6 and R_7 are the same or different and are independently selected from H, or alkyl, where alkyl may be substituted with halogen, 1 to 2 hydroxyls, 1 to 2 C_1-C_{10} alkanoyloxy, 1 to 2 C_1-C_6 alkoxy, phenyl, phenoxy, C_1-C_6 alkoxycarbonyl; or R_6 and R_7 can together form $-(CH_2)_tX_5(CH_2)_u-$ where X_5 is $-C(R_{4c})(R_{4d})-$

or -O-, t and u are the same or different and are independently 1-3;

X_3 is -C(O)-, -C(O)O-, or -$S(O)_2N(R_{4f})$;

X_4 is a bond, -O-, -OC(O)-, or -$N(R_{4g})$C(O)-;

J1 is -$(CH_2)_vCN$, -$(CH_2)_vN(T_{1a})C(O)T_1$, -$(CH_2)_vN(T_{1a})C(O)OT_1$, -$(CH_2)_vN(T_{1a})C(O)N(T_{1b})T_1$, -$(CH_2)_vSO_2T_1$, -$(CH_2)_vN(T_{1a})SO_2T_1$, -$(CH_2)_vC(O)N(T_{1a})T_1$, -$(CH_2)_vC(O)OT_1$, -$(CH_2)_vOC(O)T_1$, -$(CH_2)_vOC(O)N(T_{1a})T_1$, -$(CH_2)_vN(T_{1a})SO_2N(T_{1b})T_1$, -$(CH_2)_vOT_1$, -$(CH_2)_vSO_2N(T_{1b})T_1$, -$(CH_2)_vC(O)T_1$, or heteroaryl, with v being 0-2;

J1a is halogen, -$(CH_2)_vCN$, -$(CH_2)_vN(T_{1a})C(O)T_1$, -$(CH_2)_vC(O)N(T_{1a})T_1$, -$(CH_2)_vC(O)OT_1$, -$(CH_2)_vOT_1$, or -$(CH_2)_vC(O)T_1$, with v being 0-2;

T_1, T_{1a} and T_{1b} are the same or different and are independently selected from H, alkyl, aryl, alkaryl, or cycloalkyl each optionally substituted with halogen, hydroxyl or alkoxy; with the proviso that T_1 cannot be hydrogen when it is connected sulfur as in SO_2T_1;

7. The compound as defined in Claim 1 wherein

R_1 is alkyl, aryl, arylakyl, cycloalkyl, or cycloalkylalkyl and where these groups may be optionally substituted with a J1 group;

R_2 is alkyl, aryl, arylalkyl, or cycloalkyl, and these groups may be optionally substituted by J1a;

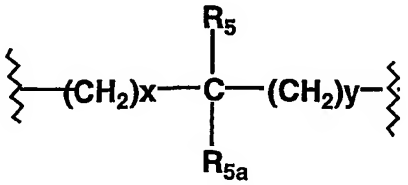
X is -NH or -NCH_3;

R_3 and R_{3a} are each H;

m is 1;

n is 0;

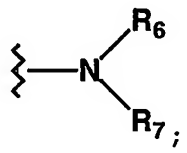
Y is



where x and y are independently 0 or 1, with the proviso that both cannot be 0;

R_5 and R_{5a} are the same or different and are independently selected from H, alkyl, or $-CF_3$; or R_5 and R_{5a} can be independently joined to one or both of R_6 and R_7 groups to form an alkylene bridge of 1 to 5 carbon atoms;

X_2 is



R_6 and R_7 are the same or different and are independently selected from H or alkyl, where alkyl may be optionally substituted with halogen, or 1 to 2 hydroxyls;

X_3 is $-C(O)-$, $-C(O)O-$, or $-S(O)_2N(R_{4f})-$;

X_4 is $-O-$, or $-OC(O)-$;

J1 is $-(CH_2)_vCN$, $-(CH_2)_vN(T_{1a})C(O)T_1$, $-(CH_2)_vN(T_{1a})C(O)OT_1$, $-(CH_2)_vN(T_{1a})C(O)N(T_{1b})T_1$, $-(CH_2)_vSO_2T_1$, $-(CH_2)_vN(T_{1a})SO_2T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOC(O)T_1$, $-(CH_2)_vOC(O)N(T_{1a})T1$, $-(CH_2)_vN(T_{1a})SO_2N(T_{1b})T_1$, $-(CH_2)_vOT_1$, $-(CH_2)_vSO_2N(T_{1a})T_1$, $-(CH_2)_vC(O)T_1$, or heteroaryl as defined below, with v being 0-2;

J1a is halogen, $-(CH_2)_vCN$, $-(CH_2)_vN(T_{1a})C(O)T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOT_1$, or $-(CH_2)_vC(O)T_1$, with v being 0-2;

T_1, T_{1a} and T_{1b} are the same or different and are independently selected from H, alkyl, aryl, or alkaryl, optionally substituted with halogen, hydroxyl or alkoxy; with the proviso that T_1 cannot be hydrogen when it is connected to sulfur as in SO_2T_1;

8. The compound as defined in Claim 1 wherein

R_1 is alkyl, aryl, arylakyl, cycloalkyl, heteroaryl or heteroarylalkyl and where these groups may be optionally substituted with a J1 group;

R_2 is aryl, arylalkyl, or cycloalkyl, where these groups may be optionally substituted with one or more J1a;

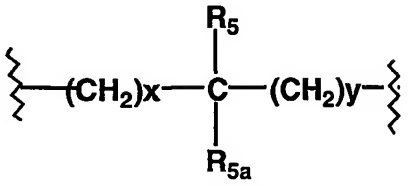
X is $-N(R_4)-$ where R_4 is H or alkyl;

R_3 and R_{3a} are each H;

m is 1;

n is 0;

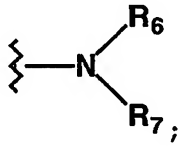
Y is



where x and y are independently 0 or 1;

R_5 and R_{5a} are the same or different and are independently selected from H, alkyl, or $-CF_3$;

X_2 is



R_6 and R_7 are the same or different and are independently selected from H or alkyl, where alkyl may be optionally substituted with halogen, or 1 to 2 hydroxyls;

X_3 is $-C(O)-$, $-C(O)O-$, $-S(O)_2-$ or $-S(O)_2N(R_{4f})-$;

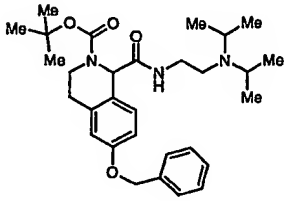
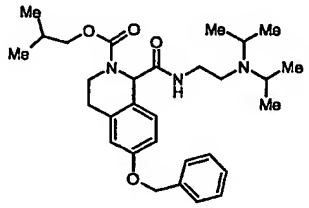
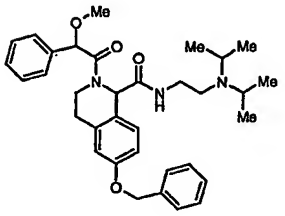
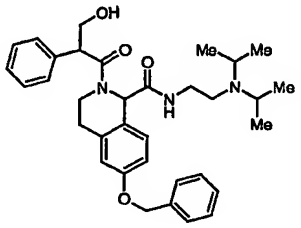
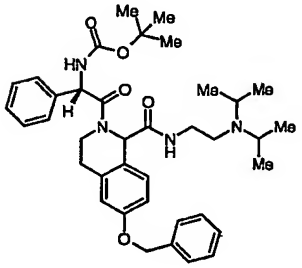
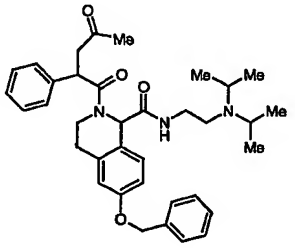
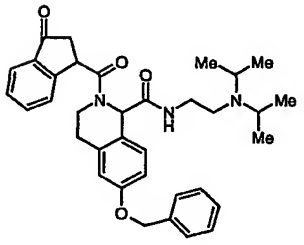
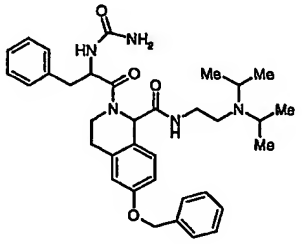
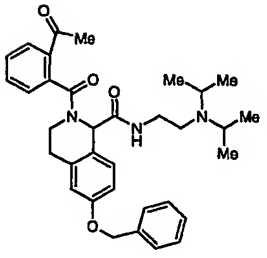
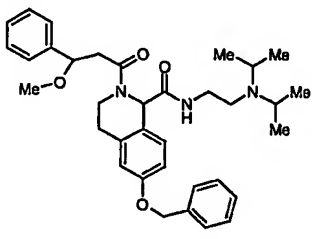
X_4 is $-O-$, or $-OC(O)-$;

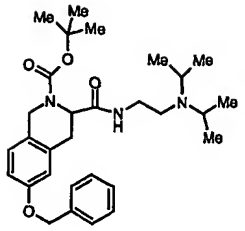
J1 is alkyl, $-(CH_2)_vCN$, $-(CH_2)_vN(T_{1a})C(O)T_1$, $-(CH_2)_vN(T_{1a})C(O)OT_1$, $-(CH_2)_vN(T_{1a})C(O)N(T_{1b})T_1$, $-(CH_2)_vSO_2T_1$, $-(CH_2)_vN(T_{1a})SO_2T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOC(O)T_1$, $-(CH_2)_vOC(O)N(T_{1a})T1$, $-(CH_2)_vN(T_{1a})SO_2N(T_{1b})T_1$, $-(CH_2)_vOT_1$, $-(CH_2)_vSO_2N(T_{1a})T_1$, $-(CH_2)_vC(O)T_1$, or heteroaryl as defined below, with v being 0-2;

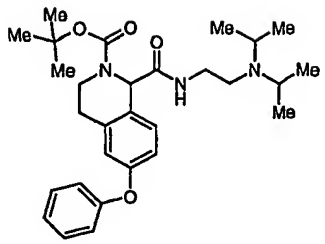
J1a is halogen, $-CF_3$, $-(CH_2)_vCN$, $-(CH_2)_vN(T_{1a})C(O)T_1$, $-(CH_2)_vC(O)N(T_{1a})T_1$, $-(CH_2)_vC(O)OT_1$, $-(CH_2)_vOT_1$, or $-(CH_2)_vC(O)T_1$, with v being 0-2;

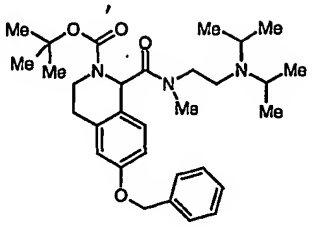
T_1, T_{1a} and T_{1b} are the same or different and are independently selected from H, alkyl, aryl, or alkaryl, optionally substituted with halogen, hydroxyl or alkoxy; with the proviso that T_1 cannot be hydrogen when it is connected to sulfur as in SO_2T_1;

9. A compound as defined in Claim 1 having the structure







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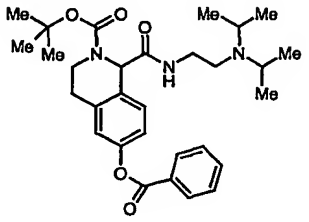

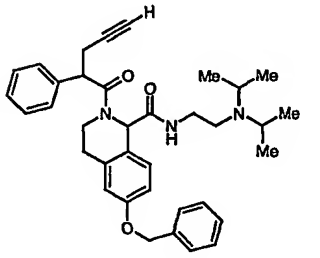

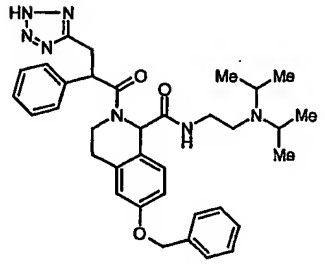

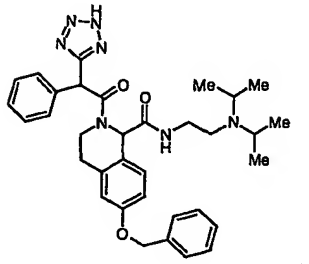

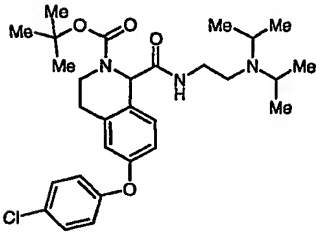

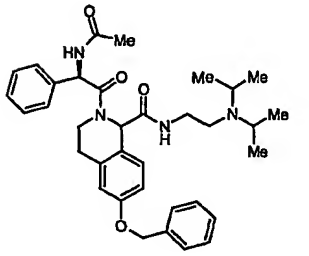

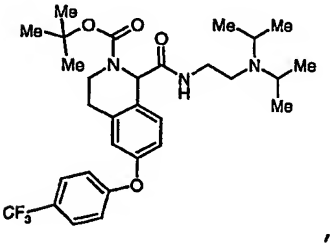

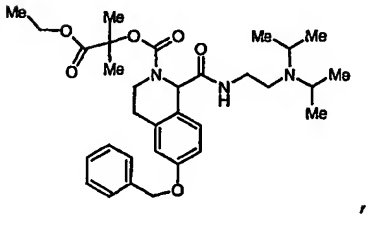

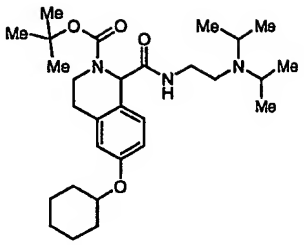

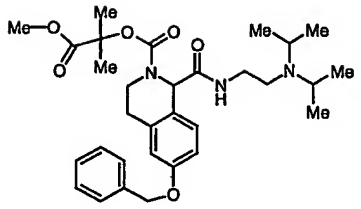

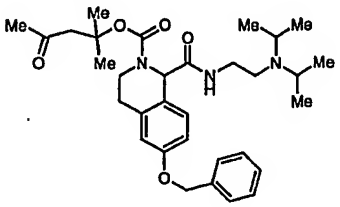

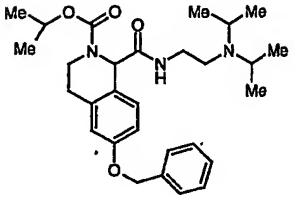

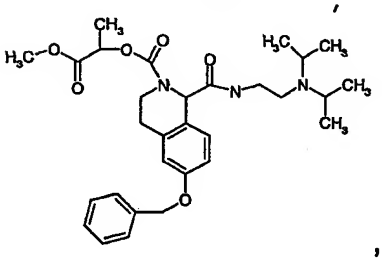

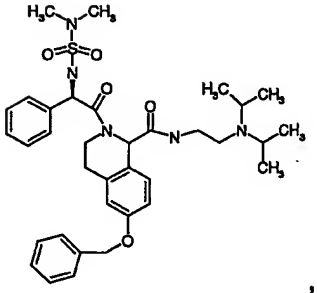

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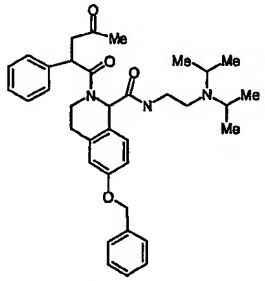

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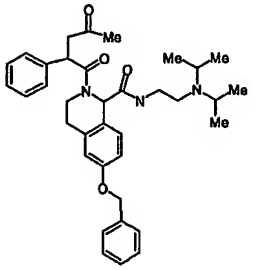

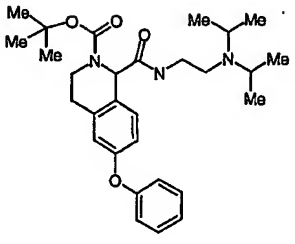

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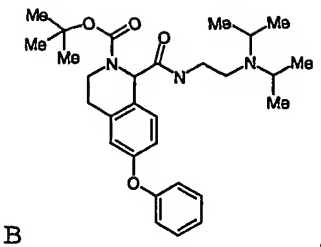

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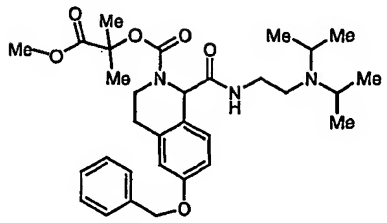

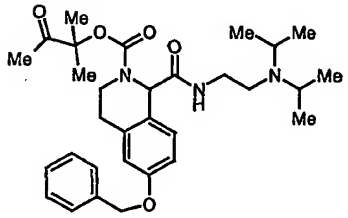

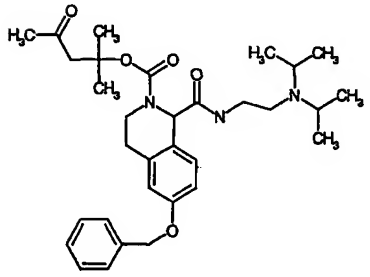

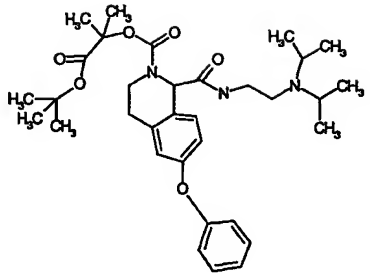

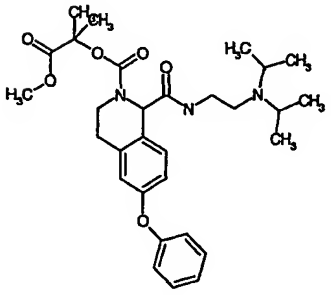

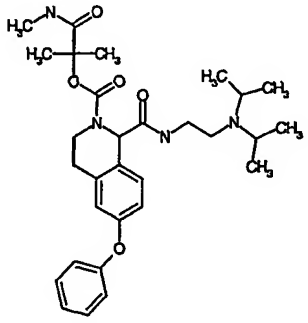

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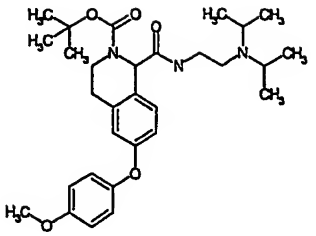

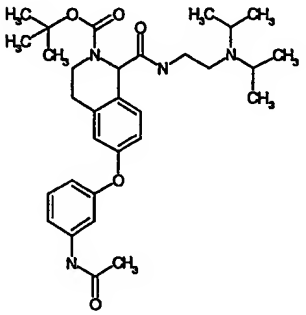

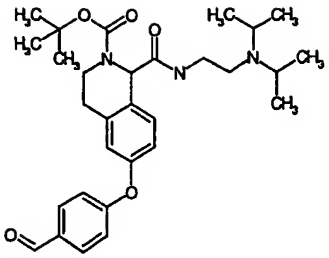

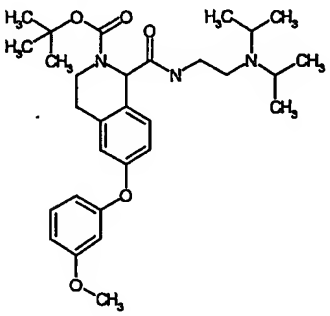

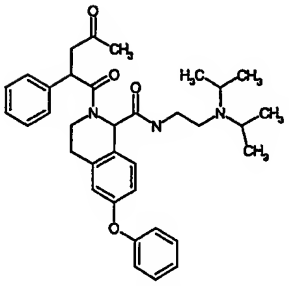

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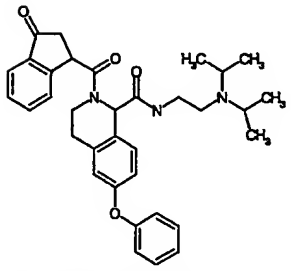

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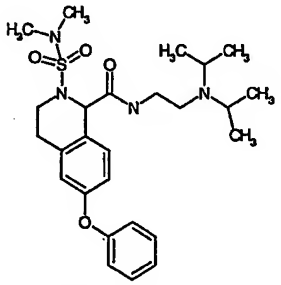

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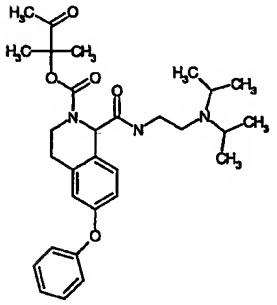
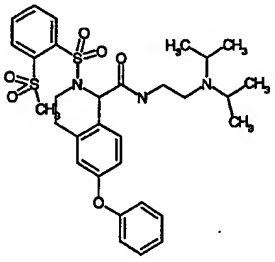
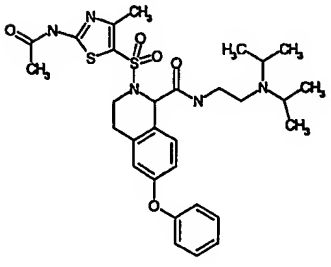
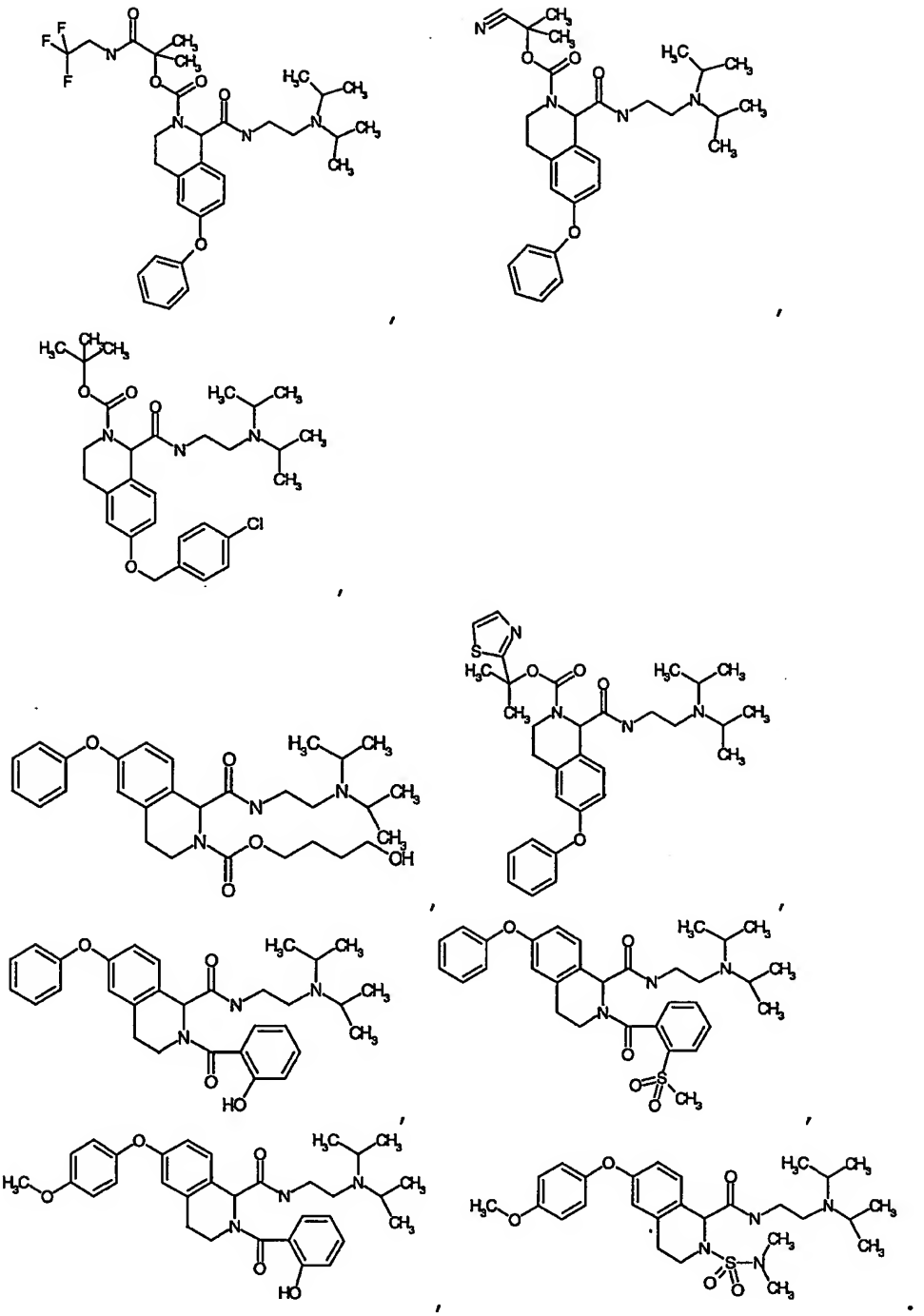
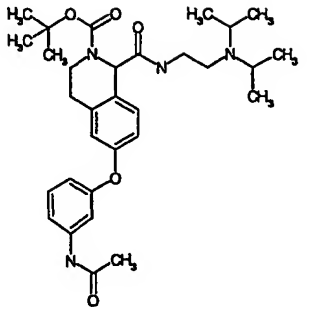








10. The compound as defined in Claim 8 having the structure



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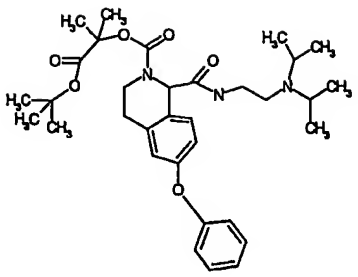

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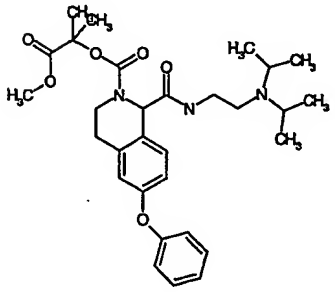

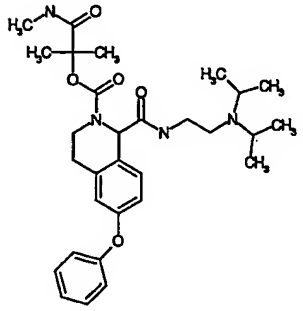

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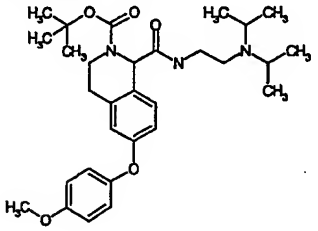

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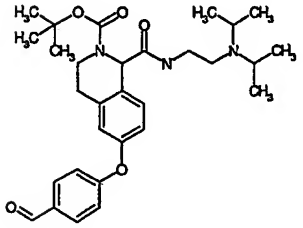

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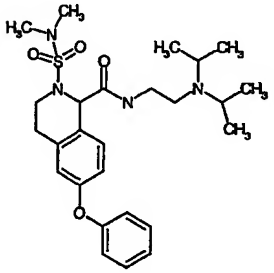

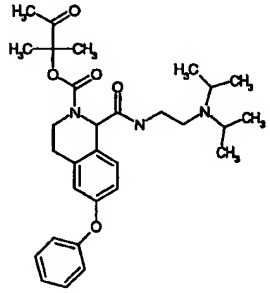

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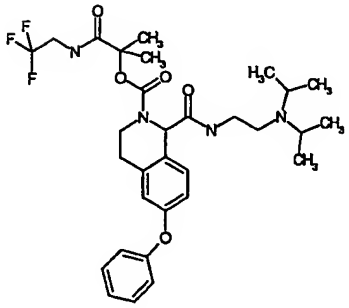

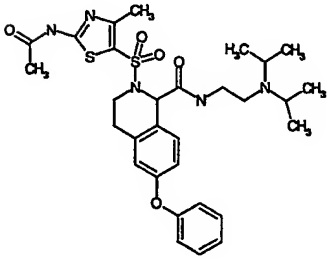

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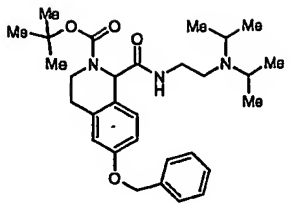

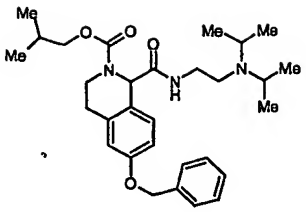

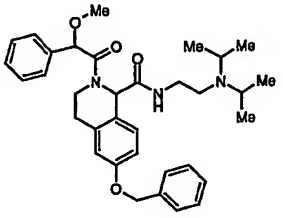

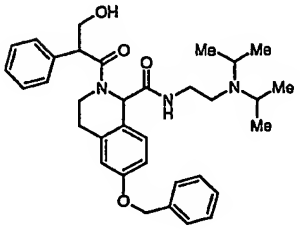

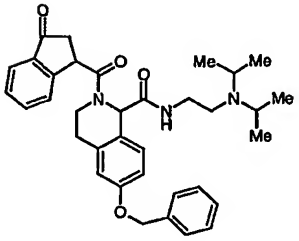

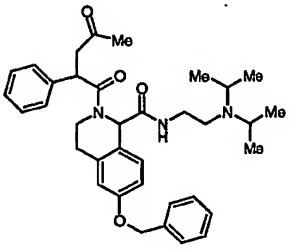

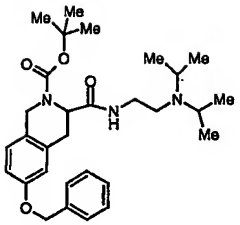

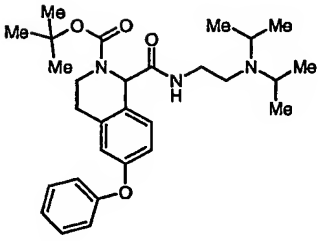

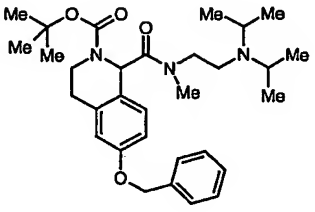

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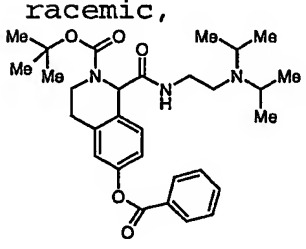

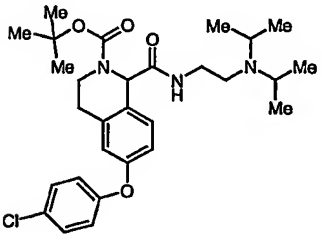

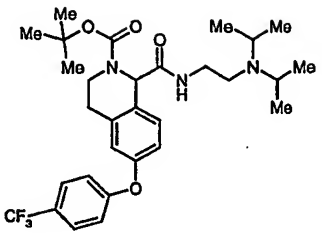

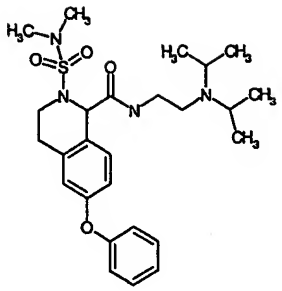

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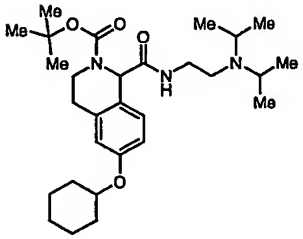

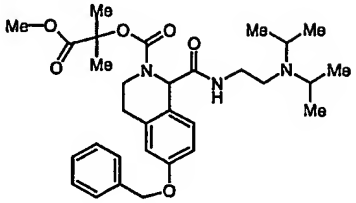

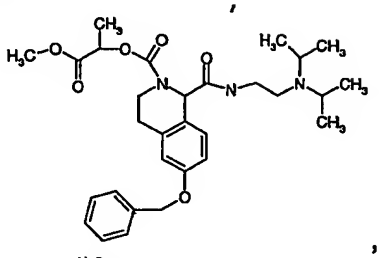

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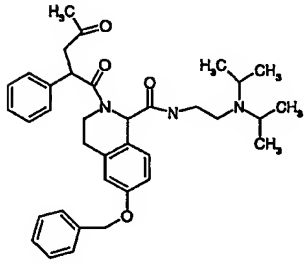

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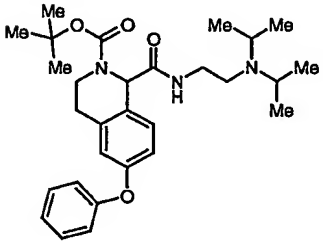

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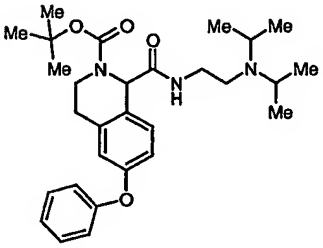

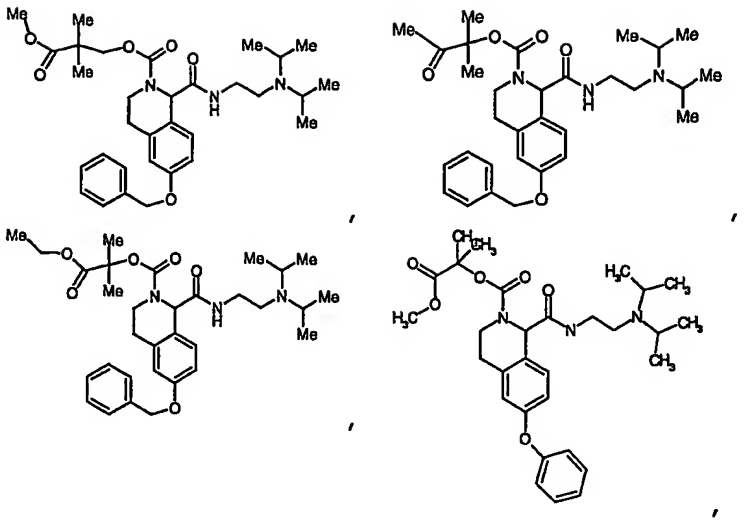

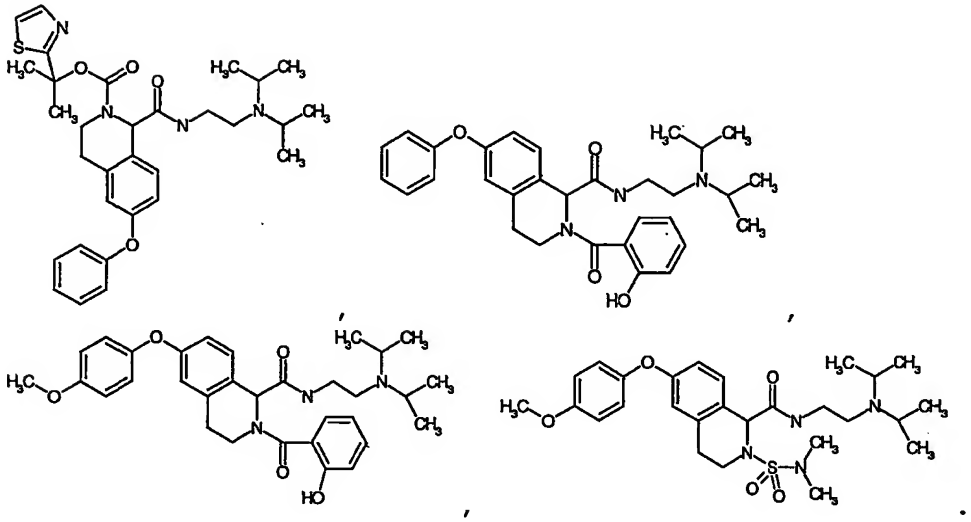

11. A pharmaceutical composition comprising a compound as defined in Claim 1 and a pharmaceutically acceptable carrier therefor.

12. A pharmaceutical composition of claim 11 further comprising at least one additional therapeutic agent selected from parathyroid hormone, bisphosphonates, estrogen, testosterone, selective estrogen receptor modulators, selective androgen receptor modulators, progestin receptor agonists, anti-diabetic agents, anti-hypertensive agents, anti-inflammatory agents, anti-osteoporosis agents, anti-obesity agents, cardiac

glycosides, cholesterol lowering agents, or thyroid mimetics.

13. A method for increasing levels of endogenous growth hormone, which comprises administering a therapeutically effective amount of a compound as defined in Claim 1 to a patient in need thereof.

14. A method for treating obesity which comprises administering a therapeutically effective amount of a compound as defined in Claim 1 to a patient in need thereof.

15. A method for treating osteoporosis which comprises administering a therapeutically effective amount of a compound as defined in Claim 1 to a patient in need thereof.

16. A method for treating renal disease which comprises administering a therapeutically effective amount of a compound as defined in Claim 1 to a patient in need thereof.

17. A method for treating congestive heart failure, cardiac myopathy or cardiac dysfunction associated with valvular disease which comprises administering a therapeutically effective amount of a compound as defined in Claim 1 to a patient in need thereof.

18. A method for treating cachexia which comprises administering a therapeutically effective amount of a compound as defined in Claim 1 to a patient in need thereof.

19. A method for treating HIV wasting syndrome, muscular atrophy, lipodistrophy, long term critical illness,

sarcopenia, stimulating wound healing and/or the immune system, increasing muscle mass and/or strength, maintaining muscle strength and function in the elderly, or treating frailty or ARFD in the elderly which comprises administering a therapeutically effective amount of a compound as defined in Claim 1 to a patient in need thereof.

20. A method for treating anorexia which comprises administering a therapeutically effective amount of a compound as defined in Claim 1 to a patient in need thereof.

21. A method for treating sleep disorders which comprises administering a therapeutically effective amount of a compound as defined in Claim 1 to a patient in need thereof.

22. A method for treating depression which comprises administering a therapeutically effective amount of a compound as defined in Claim 1 to a patient in need thereof.

23. A method for improving cognitive function which comprises administering a therapeutically effective amount of a compound as defined in Claim 1 to a patient in need thereof.

24. A method for improving the immune response to vaccination which comprises administering a therapeutically effective amount of a compound as defined in Claim 1 to a patient in need thereof.

25. A method for accelerating the recovery of hip fracture which comprises administering a therapeutically effective amount of a compound as defined in Claim 1 to a patient in need thereof.

26. A method for treating Syndrome X, which comprises administering a therapeutically effective amount of a compound as defined in Claim 1 to a patient in need thereof.

27. A method for treating diabetes and/or increasing lean body mass, which comprises administering a therapeutically effective amount of a compound as defined in Claim 1 to a patient in need thereof.

28. A pharmaceutical composition of claim 11 further comprising at least one nutritional supplement.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/14709

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D217/26 C07D209/44 C07D223/16 C07K5/06 C07D417/12
A61K31/472 A61P3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 24398 A (BRISTOL MYERS SQUIBB CO) 4 May 2000 (2000-05-04) claims	1-28
A	WO 00 10975 A (TOKUNAGA TERUHISA ;HUME W EWAN (JP); KUMAGAI KAZUO (JP); UEKI YASU) 2 March 2000 (2000-03-02) cited in the application claims	1-28
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 August 2001	06/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax (+31–70) 340–3016	Chouly, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92 16524 A (MERCK & CO INC) 1 October 1992 (1992-10-01) claims & US 5 206 235 A 27 April 1993 (1993-04-27) cited in the application	1-28
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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